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Definition of Specimen "Minimum Volume"

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

Animal Specimens
We do not accept animal specimens for laboratory testing.

Billing
Client—Each month you will receive an itemized invoice/statement which will indicate the date of service, patient name, CPT code, test name, and test charge. Payment terms are net 30 days. When making payment, please include our invoice number on your check to ensure proper credit to your account.

Patient—Mayo Clinic Laboratories does not routinely bill patient’s insurance; however, if you have made advanced arrangements to have Mayo Clinic Laboratories bill your patient’s insurance, please include the following required billing information: responsible party, patient’s name, current address, zip code, phone number, Social Security number, and diagnosis code. Providing this information will avoid additional correspondence to your office at some later date. Please advise your patients that they will receive a bill for laboratory services from Mayo Clinic Laboratories for any personal responsibility after insurance payment. VISA® and MasterCard® are acceptable forms of payment.

Billing—CPT Coding
It is your responsibility to determine correct CPT codes to use for billing. While this catalog lists CPT codes in an effort to provide some guidance, CPT codes listed only reflect our interpretation of CPT coding requirements and are not necessarily correct. Particularly, in the case of a test involving several component tests, this catalog attempts to provide a comprehensive list of CPT codes for all of the possible components of the test. Only a subset of component tests may be performed on your specimen. You should verify accuracy of codes listed. Where multiple codes are listed, you should select codes for tests actually performed on your specimen. MAYO CLINIC LABORATORIES ASSUMES NO RESPONSIBILITY FOR BILLING ERRORS DUE TO RELIANCE ON CPT CODES LISTED IN THIS CATALOG. For further reference, please consult the CPT Coding Manual published by the American Medical Association. If you have any questions regarding use of a code, please contact your local Medicare carrier.

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

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

Chain-of-Custody
Chain-of-custody, a record of disposition of a specimen to document who collected it, who handled it, and who performed the analysis, is necessary when results are to be used in a court of law. Mayo Clinic Laboratories has developed packaging and shipping materials that satisfy legal requirements for chain-of-custody. This service is only offered for drug testing.
Compliance Policies
Mayo Clinic Laboratories is committed to compliance with applicable laws and regulations such as the Clinical Laboratory Improvement Amendments (CLIA). Regulatory agencies that oversee our compliance include, but are not limited to, the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Department of Transportation (DOT). Mayo Clinic Laboratories develops, implements, and maintains policies, processes, and procedures throughout our organization which are designed to meet relevant requirements. We expect clients utilizing our services will ensure their compliance with patient confidentiality, diagnosis coding, anti-kick back statutes, professional courtesy, CPT-4 coding, CLIA proficiency testing, and other similar regulatory requirements. Also see “Accreditation and Licensure,” “HIPAA Compliance,” and “Reportable Disease.”

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

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

- Mayo Clinic Laboratories’ accession ID number for specimen; or
- Client account number from Mayo Clinic Laboratories along with patient name; or
- Client accession ID number interfaced to Mayo Clinic Laboratories; or
- Identification by individual that he or she is, in fact, “referring physician” identified on requisition form by Mayo Clinic Laboratories’ client

Under federal regulations, we are only authorized to release results to ordering physicians or health care providers responsible for the individual patient’s care. Third parties requesting results including requests directly from the patient are directed to the ordering facility. We appreciate your assistance in helping Mayo Clinic Laboratories preserve patient confidentiality. Provision of appropriate identifiers will greatly assist prompt and accurate response to inquiries and reporting.

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

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

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

Action Taken when a Result is Obtained that Exceeds the Limit Defined by the DLMP Critical Values List—In addition to the normal results reporting (eg, fax, interface), Mayo Clinic Laboratories’ staff telephone the ordering physician or the client-provided contact number within 60 minutes following laboratory release of the critical test result(s). In the event that contact is not made within the 60-minute period, we continue to telephone until the designated party is reached and the result is conveyed in compliance and adherence to the CAP.
Semi-Urgent Results—Semi-Urgent Results are defined by Mayo Clinic as those infectious disease-related results that are needed promptly to avoid potentially serious health consequences for the patient (or in the case of contagious diseases, potentially serious health consequences to other persons exposed to the patient) if not acknowledged and/or treated by the physician. While not included on the Critical Values List, this information is deemed important to patient care in compliance and adherence to the CAP.

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

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

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

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

Fee Changes
Fees are subject to change without notification and complete pricing per accession number is available once accession number is final. Specific client fees are available by calling Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 or by visiting mayocliniclabs.com.

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

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

“Framework for Quality” is composed of 12 “Quality System Essentials.” The policies, processes, and procedures associated with the “Quality System Essentials” can be applied to all operations in the path of workflow (eg, pre-analytical, analytical, and post-analytical). Performance is measured through constant monitoring of activities in the path of workflow and comparing performance through benchmarking internal and external quality indicators and proficiency testing.

Data generated by quality indicators drives process improvement initiatives to seek resolutions to system-wide problems. Mayo Clinic Laboratories utilizes “Failure Modes and Effects Analysis (FMEA),” “Plan Do Study Act (PDSA),” “LEAN,” “Root Cause Analysis,” and “Six Sigma” quality improvement tools to determine appropriate remedial, corrective, and preventive actions.
Quality Indicators—Mayo Clinic Laboratories produces hundreds of Key Performance Indicators for our business and operational areas, and we review them regularly to ensure that we continue to maintain our high standards. A sampling of these metrics includes:

- Pre-analytic performance indicators
  - Lost specimens*
  - On-time delivery
  - Special handling calls
  - Specimen acceptability*
  - Specimen identification*
  - Incoming defects*
- Analytic performance indicators
  - Proficiency testing
  - Quality control
  - Turnaround (analytic) times
  - Quantity-not-sufficient (QNS) specimens*
- Post-analytic performance indicators
  - Revised reports*
  - Critical value reports*
- Operational performance indicators
  - Incoming call resolution*
  - Incoming call abandon rate
  - Call completion rate
  - Call in-queue monitoring
  - Customer complaints
  - Customer satisfaction surveys

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

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

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

Infectious Material
The Centers for Disease Control (CDC) in its regulations of July 21, 1980, has listed organisms and diseases for which special packaging and labeling must be applied. Required special containers and packaging instructions can be obtained from us by using the “Request for Supplies” form or by ordering from the online Supply Catalog at mayocliniclabs.com/customer-service/supplies/index.php.

Shipping regulations require that infectious substances affecting humans be shipped in a special manner. See “Infectious Material.” A copy of the regulations can be requested from the International Air Transport Association (IATA); they may be contacted by phone at 514-390-6770 or by fax at 514-874-2660.

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

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

**Patient Safety Goals**
One of The Joint Commission National Patient Safety goals for the Laboratory Services Program is to improve the accuracy of patient identification by using at least 2 patient identifiers when providing care, treatment, or services.

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

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

**Parallel Testing**
Parallel testing may be appropriate in some cases to re-establish patient baseline results when converting to a new methodology at Mayo Clinic Laboratories. Contact your Regional Manager at 800-533-1710 or 507-266-5700 or mayocliniclabs.com for further information.

**Proficiency Testing**
We are a College of American Pathologists (CAP)-accredited, CLIA-licensed facility that voluntarily participates in many diverse external and internal proficiency testing programs. It is Mayo Clinic Laboratories’ expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing (42 CFR 493.801), including a prohibition on discussion about samples or results and sharing of proficiency testing materials with Mayo Clinic Laboratories during the active survey period.

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

It is Mayo Clinic Laboratories’ expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing including a prohibition on discussion about samples or results and sharing of proficiency materials with Mayo Clinic Laboratories during the active survey period.
testing materials with Mayo Clinic Laboratories during the active survey period. Referring of specimens is acceptable for comparison purposes when an approved proficiency-testing program is not available for a given analyte.

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

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

**Referral of Tests to Another Laboratory**
Mayo Clinic Laboratories forwards tests to other laboratories as a service to its clients. This service should in no way represent an endorsement of such test or referral laboratory or warrant any specific performance for such test. Mayo Clinic Laboratories will invoice for all testing referred to another laboratory at the price charged to Mayo Clinic Laboratories. In addition, Mayo Clinic Laboratories will charge an administrative fee per test for such referral services.

**Reflex Testing**
Mayo Clinic Laboratories identifies tests that reflex when medically appropriate. In many cases, Mayo Clinic Laboratories offers components of reflex tests individually as well as together. Clients should familiarize themselves with the test offerings and make a decision whether to order a reflex test or an individual component. Clients, who order a reflex test, can request to receive an “Additional Testing Notification Report” which indicates the additional testing that has been performed. This report will be faxed to the client. Clients who wish to receive the “Additional Testing Notification Report” should contact their Regional Manager or Regional Service Representative.

**Reportable Disease**
Mayo Clinic Laboratories, in compliance with and adherence to the College of American Pathologists (CAP) Laboratory General Checklist (CAP GEN. 20373) strives to comply with laboratory reporting requirements for each state health department regarding reportable disease conditions. We report by mail, fax, and/or electronically, depending upon the specific state health department regulations. Clients shall be responsible for compliance with any state specific statutes concerning reportable conditions, including, but not limited to, birth defects registries or chromosomal abnormality registries. This may also include providing patient address/demographic information. Mayo Clinic Laboratories’ reporting does not replace the client or physician responsibility to report as per specific state statues.

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

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

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

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

There is a nominal charge associated with any special handling.

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

Specimen Identification Policy
In compliance with and adherence to the CAP and the Joint Commission’s 2008 Patient Safety Goals (1A), Mayo Clinic Laboratories’ policy states that all specimens received for testing must be correctly and adequately labeled to assure positive identification. Specimens must have 2 person-specific identifiers on the patient label. Person-specific identifiers may include: accession number, patient’s first and last name, unique identifying number (eg, medical record number), or date of birth. Specimens are considered mislabeled when there is a mismatch between the person-specific identifiers on the specimen and information accompanying the specimen (eg, computer system, requisition form, additional paperwork).

When insufficient or inconsistent identification is submitted, Mayo Clinic Laboratories will recommend that a new specimen be obtained, if feasible.

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

Please review the following conditions prior to submitting a specimen to Mayo Clinic Laboratories:
- Full 24 hours for timed urine collection
- pH of urine
- Lack of hemolysis/lipemia
- Specimen type (plasma, serum, whole blood, etc.)
- Specimen volume
- Patient information requested
- Proper identification of patient/specimen
- Specimen container (metal-free, separation gel, appropriate preservative, etc.)
- Transport medium
- Temperature (ambient, frozen, refrigerated)

Specimen Volume
The “Specimen Required” section of each test includes 2 volumes - preferred volume and minimum volume. Preferred volume has been established to optimize testing and allows the laboratory to quickly process specimen containers, present containers to instruments, perform test, and repeat test, if necessary. Many of our testing processes are fully automated; and as a result, this volume allows hands-free testing and our quickest turnaround time (TAT). Since patient values are frequently abnormal, repeat testing, dilutions, or other specimen manipulations often are required to obtain a reliable, reportable result. Our preferred specimen requirements allow expeditious testing and reporting.

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

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

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

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

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

Test Development Process
Mayo Clinic Laboratories serves patients and health care providers from Mayo Clinic, Mayo Health System, and our reference laboratory clients worldwide. We are dedicated to providing clinically useful, cost-effective testing strategies for patient care. Development, validation, and implementation of new and improved laboratory methods are major components of that commitment.

Each assay utilized at Mayo Clinic, whether developed on site or by others, undergoes an extensive validation and performance documentation period before the test becomes available for clinical use. Validations follow a standard protocol that includes:
- Accuracy
• Precision
• Sensitivity
• Specificity and interferences
• Reportable range
• Specimen stability
• Specimen type comparisons, if applicable
• Urine preservative studies: stability at ambient, refrigerated, and frozen temperatures and with 7 preservatives; at 1, 3, and 7 days
• Comparative evaluation with current and potential methods, if applicable
• Reference intervals: reference intervals provided by Mayo Clinic Laboratories are derived from studies performed in our laboratories or adopted from the manufacturer package insert after internal verification. When reference intervals are obtained from other sources, the source is indicated in the “Reference Values” field.
• Workload recording
• Limitations of the assay
• Clinical utility and interpretation: written by Mayo Clinic medical experts, electronically available (MayoAccess™)

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

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

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

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

Unlisted Tests
Mayo Clinic Laboratories does not list all available test offerings in the paper catalog. New procedures are developed throughout the year; therefore, some tests are not listed in this catalog. Although we do not usually accept referred tests of a more routine type, special arrangements may be made to provide your laboratory with temporary support during times of special need such as sustained instrumentation failure. For information about unlisted tests, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.
1,25-Dihydroxyvitamin D, Serum

Clinical Information: Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols, which act as hormones. In the presence of renal disease or hypercalcemia, testing of 1,25-dihydroxy vitamin D (DHVD) might be needed to adequately assess vitamin D status. The 25-hydroxyvitamin D (25HDN) test (25HDN / 25-Hydroxyvitamin D2 and D3, Serum) in serum is otherwise the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. Vitamin D compounds in the body are exogenously derived by dietary means; from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. 25HDN is subsequently formed by hydroxylation (CYP2R1) in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD, the active metabolite of 25HDN. 1-Alpha-hydroxylation (CYP27B1) occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process, regulated by parathyroid hormone (PTH), might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents over production of DHVD and resultant vitamin D toxicity. DHVD stimulates calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and PTH. DHVD promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the parathyroid glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, DHVD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs. DHVD levels are decreased in hypoparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in chronic renal failure.

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

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

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

Females:
<16 years: 24-86 pg/mL
For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html


SFUNG

604094

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

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

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

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

Reference Values:
FUNGITELL QUANTITATIVE VALUE:
<60 pg/mL

FUNGITELL QUALITATIVE RESULT:
Negative

Reference values apply to all ages.


11-Deoxycorticosterone, Serum

Clinical Information: The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions).

11-Deoxycorticosterone represents the last intermediate in the mineral corticoid pathway that has negligible mineral corticoid activity. It is converted by 11-beta-hydroxylase 2 (CYP11B2) or by 11-beta-hydroxylase 1 (CYP11B1) to the first mineral corticoids with significant activity, corticosterone. Corticosterone is in turn converted to 18-hydroxycorticosterone and finally to aldosterone, the most active mineral corticoid. Both of these reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase activity. The major diagnostic utility of measurement of steroid synthesis intermediates is in diagnosing disorders of steroid synthesis, in particular, congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17-alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases), and those with the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies, might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases), are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, in hirsutism, polycystic ovarian syndrome, or infertility, as well as in possible premature adrenarche and pubarche in both genders. Measurement of the various precursors of mature mineral corticoids and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of 11-deoxycorticosterone and its glucocorticoid pendant, 11-deoxycortisol (also known as compound S), is aimed at diagnosing: -CYP11B1 deficiency (associated with cortisol deficiency) -The rarer CYP11B2 deficiency (no cortisol deficiency) -The yet less common glucocorticoid-responsive hyperaldosteronism (where expression of the gene CYP11B2 is driven by the CYP11B1 promoter, thus making it responsive to adrenocorticotropic hormone: ACTH rather than renin) For other forms of CAH, the following tests might be relevant: -11-Hydroxylase deficiency: - DOC / 11-Deoxycortisol, Serum - CORTC / Corticosterone, Serum - HYD18 /
Hydroxycorticosterone, 18 - PRA / Renin Activity, Plasma - ALDS / Aldosterone, Serum
-3-Beta-steroid-dehydrogenase deficiency: - 17PRN / Pregnenolone and 17-Hydroxypregnenolone,
Serum -17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): - PREGN /
Pregnenolone, Serum - 17OHP / 17-Hydroxypregnenolone, Serum - PGSN / Progesterone, Serum -
OHPG / 17-Hydroxyprogesterone, Serum - DHEA / Dehydroepiandrosterone (DHEA), Serum - ANST /
Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. In the diagnosis
of suspected 11-hydroxylase deficiency and glucocorticoid-responsive hyperaldosteronism, this test
should be used in conjunction with measurements of 11-deoxycortisol, corticosterone,
18-hydroxycorticosterone, cortisol, renin, and aldosterone.

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

Interpretation: In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will
be low (usually <7 microgram/dL for a morning draw). 11-Deoxy cortisol and 11-deoxycorticosterone are
elevated, usually to at least 2 to 3 times (more typically 20-300 times) the upper limit of the normal
reference range on a morning blood draw. Elevations in 11-deoxycortisol are usually relatively greater
than those of 11-deoxycorticosterone, because of the presence of intact 11 beta-hydroxylase 2
(CYP11B2). For this reason, serum concentrations of all potent mineral corticoids (corticosterone,
18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range.
Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in
interpreting the mineral corticoid results in infants younger than 7 days; mineral corticoid levels are often
substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult
levels by week 1. Mild cases of CYP11B1 deficiency might require adrenocorticotropic hormone
(ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum
11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250
microgram of ACTH1-24 will usually exceed 20 ng/mL, or demonstrate at least a 4-fold rise. Such
increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response
will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually
normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more
profoundly than in CYP11B1 deficiency, while 11-deoxy cortisol may or may not be significantly
elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum
18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if
the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone
concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase
function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the
CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive
hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2
gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are
significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of
ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol
(an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol
conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of
18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients.
Ultimate diagnostic confirmation comes from showing direct responsiveness of mineral corticoid
production to ACTH1-24 injection. Normally, this has little if any effect on corticosterone,
18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by
showing that mineral corticoid levels fall after administration of dexamethasone. Sex steroid levels are
moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced in
CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually
normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone
concentrations well in excess of 1000 ng/dL. For the few patients with levels in the range of higher than
630 ng/dL (upper limit of reference range for newborns) to 2000 or 3000 ng/dL, it might be prudent to
consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum
androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYB11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylase to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires via 11-hydroxylation of 17-hydroxyprogesterone. Cautions At birth, the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis are activated and all adrenal steroids are high, including mineral corticoids and sex steroids and their precursors. In preterm infants, elevations can be even more pronounced due to illness and stress. In doubtful cases, when the initial test was performed on a just-born baby, repeat testing a few days or weeks later is advised. Adrenocorticotrophic hormone (ACTH)1-24 testing has a low, but definite risk of drug and allergic reactions and should, therefore, only be performed under the supervision of a physician in an environment that guarantees the patient's safety, typically an endocrine, or other centralized, testing center. Interpretation of ACTH1-24 testing in the context of diagnosis of congenital adrenal hyperplasia (CAH) requires considerable experience, in particular for the less common variants of CAH, such as 11-hydroxylase deficiency or 3-beta-hydroxysteroid dehydrogenase (3beta-HSD deficiency), for which very few, if any, reliable normative data exist. For the even rarer enzyme defects, such as deficiencies of StAR (steroidogenic acute regulatory protein), 20,22 desmolase, 17a-hydroxylase/17-lyase, and 17-beta-hydroxysteroid dehydrogenase (17beta-HSD), there are only case reports. Expert opinion from a pediatric endocrinologist with experience in CAH should, therefore, be sought.

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

11 beta-hydroxylase 

11-deoxycortisol

Cortisol Compound S is typically increased when adrenocorticotropic hormone (ACTH) levels are increased (eg, Cushing disease, ACTH-producing tumors) or in 11 beta-hydroxylase deficiency, a rare subform of congenital adrenal hyperplasia (CAH).

In CAH due to 11 beta-hydroxylase deficiency, cortisol levels are low, resulting in increased pituitary ACTH production and increased serum and urine 11-deoxycortisol levels. Pharmacological blockade of 11 beta-hydroxylase with metyrapone can be used to assess the function of the hypothalamic-pituitary-adrenal axis (HPA). In this procedure metyrapone is administered to patients, and serum 11-deoxycortisol levels or urinary 17-hydroxy steroid levels are measured either at baseline (midnight) and 8 hours later (overnight test), or at baseline and once per day during a 2-day metyrapone test (4-times a day metyrapone administration over 2 days). Two-day metyrapone testing has been largely abandoned because of the logistical problems of multiple timed urine and blood collections and the fact that overnight testing provides very similar results. In either case, the normal response to metyrapone administration is a fall in serum cortisol levels, triggering a rise in pituitary ACTH secretion, which, in turn, leads to a rise in 11-deoxycortisol levels due to the ongoing 11-deoxycortisol-to-cortisol conversion block. In the diagnostic workup of suspected adrenal insufficiency, the results of overnight metyrapone testing correlate closely with the gold standard of HPA-axis assessment, insulin hypoglycemia testing. Combining 11-deoxycortisol measurements with ACTH measurements during metyrapone testing further enhances the performance of the test. Impairment of any component of the HPA-axis results in a subnormal rise in 11-deoxycortisol levels.

By contrast, standard-dose or low-dose ACTH(1-24) (cosyntropin)-stimulation testing, which forms the backbone for diagnosis of primary adrenal failure (Addison disease), only assess the ability of the adrenal cells to respond to ACTH stimulation. While this allows unequivocal diagnosis of primary adrenal failure, in the setting of secondary or tertiary adrenal insufficiency, metyrapone testing is more sensitive and specific than either standard-dose or low-dose ACTH(1-24)-stimulation testing. Metyrapone testing is also sometimes employed in the differential diagnosis of Cushing syndrome. In Cushing disease (pituitary-dependent ACTH overproduction), the ACTH-hypersecreting pituitary tissue remains responsive to the usual feedback stimuli, just at a higher "set-point" than in the normal state, resulting in increased ACTH secretion and 11-deoxycortisol production after metyrapone administration. By contrast, in Cushing syndrome due to primary adrenal corticosteroid oversecretion or ectopic ACTH secretion, pituitary ACTH production is appropriately shut down and there is usually no further rise in ACTH and, hence 11-deoxycortisol, after metyrapone administration. The metyrapone test has similar sensitivity and specificity to the high-dose dexamethasone suppression test in the differential diagnosis of Cushing disease, but is less widely used because of the lack of availability of an easy, automated 11-deoxycortisol assay. In recent years, both tests have been supplanted to some degree by corticotropin-releasing hormone (CRH)-stimulation testing with petrosal sinus serum ACTH sampling. See Steroid Pathways in Special Instructions.

**Useful For:**

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

**Interpretation:** In a patient suspected of having congenital adrenal hyperplasia (CAH), elevated serum 11-deoxycortisol levels indicate possible 11 beta-hydroxylase deficiency. However, not all patients will show baseline elevations in serum 11-deoxycortisol levels. In a significant proportion of cases, increases in 11-deoxycortisol levels are only apparent after adrenocorticotropic hormone (ACTH) stimulation. Serum 11-deoxycortisol levels below 1,700 ng/dL 8 hours after metyrapone administration is indicative of probable adrenal insufficiency. The test cannot reliably distinguish between primary and secondary or tertiary causes of adrenal failure, as neither patients with pituitary failure, nor those with primary adrenocortical failure, tend to show an increase of 11-deoxycortisol levels after metyrapone is administered. See Steroid Pathways in Special Instructions.

**Reference Values:**

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

For SI unit Reference Values, see [https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html](https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html)
**Clinical References:**


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**F11DX 75673**

**11-Deoxycortisol Reference Values:**

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<thead>
<tr>
<th>Age</th>
<th>Range (ng/dL)</th>
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<tbody>
<tr>
<td>Premature (26 - 28 weeks) Day 4</td>
<td>110-1376</td>
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<td>Premature (31 - 35 weeks) Day 4</td>
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<td>Newborn Day 3</td>
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<tr>
<td>Prepubertal 8 AM</td>
<td>20-155</td>
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<td>Prepubertal Children and Adults 8 AM</td>
<td>12-158</td>
</tr>
</tbody>
</table>

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**THCMX 62744**

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

**Clinical Information:**

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

Interpretation: The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid > or =10 ng/g is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by LC-MS/MS: 10 ng/g

Clinical References:

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

Useful For: Detection of in utero drug exposure to marijuana (tetrahydrocannabinol) up to 5 months before birth.
**Interpretation:** The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid at 10 ng/g or greater is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by LC-MS/MS: 10 ng/g

**Clinical References:**

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**F143P 14-3-3 eta Protein**

**Clinical Information:** The 14-3-3 protein appears to contribute to the pathologic process of joint erosion and, as such, is an emerging biomarker of joint damage in rheumatoid arthritis (RA) and psoriatic arthritis. Concentrations are significantly higher in people with active joint disease than in those with inactive RA or psoriasis without arthritis. Measurement of 14-3-3 complements RF and CCP antibody tests and may improve diagnostic sensitivity.

**Reference Values:**
<0.2 ng/mL

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**17OHP 17-Hydroxyprogrenolone, Serum**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxysteroid dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at the position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxysteroid dehydrogenase: 3-beta-HSD). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHHP) from 17-hydroxyprogrenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxyprogrenolone and pregnenolone levels may increase, and 17-OHHP and progesterone levels, respectively, are low. Dehydroepiandrosterone (DHEA) is also converted to androstenedione by 3-beta-HSD and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for
21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternatively, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxyprogrenenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** As an ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase (3-beta-HSD) deficiency Analysis for 17-hydroxyprogrenenolone is also useful as part of a battery of tests to evaluate females with hirsutism or infertility; both can result from adult-onset CAH.

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

**Reference Values:**

**CHILDREN***

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

**TANNER STAGES**
- Stage I: <209 ng/dL
- Stage II: <356 ng/dL
- Stage III: <451 ng/dL
- Stage IV-V: 35-478 ng/dL

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

**TANNER STAGES**
Stage I: <236 ng/dL
Stage II: <368 ng/dL
Stage III: <431 ng/dL
Stage IV-V: <413 ng/dL

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


**Clinical References:**

**OHPG 9231**

**17-Hydroxyprogesterone, Serum**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. The resulting hormone imbalances with reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (OHPG) and androgens can lead to life-threatening, salt-wasting crisis in the newborn period and incorrect gender assignment of virtualized females. Adult-onset CAH may result in hirsutism or infertility in females. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 position to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequent increased pituitary release of ACTH increases production of OHPG. But, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-hydroxysteroid dehydrogenase type 2 (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone respectively. OHPG is bound to both corticosteroid binding globulin and albumin and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests are available to diagnose disorders or steroid metabolism than pregnanetriol measurement. Most (90%) cases of CAH are due to mutations in the steroid 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione (ANST / Androstenedione, Serum) with decreased cortisol (CINP / Cortisol, Serum, LC-MS/MS). By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (FD0C / Deoxy cortisolone [DOC], Serum), respectively, are necessary for diagnosis. CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of OHPG, androstenedione, and cortisol. See Steroid Pathways in Special Instructions.

**Useful For:** The analysis of 17-hydroxyprogesterone (17-OHPG) is 1 of the 3 analytes along with cortisol and androstenedione, that constitutes the best screening test for congenital adrenal hyperplasia (CAH), caused by either 11- or 21-hydroxylase deficiency. Analysis for 17-OHPG is also useful as part of a battery of tests to evaluate females with hirsutism or infertility; both can result from adult-onset CAH.
**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and ideally also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels of up to 100 ng/dL are usually regarded as acceptable. See Steroid Pathways in Special Instructions.

**Reference Values:**

**Children**
- Preterm infants
  - Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL.
- Term infants
  - 0-28 days: <630 ng/dL
  - Levels fall from newborn (<630 ng/dL) to prepubertal gradually within 6 months.
- Prepubertal males: <110 ng/dL
- Prepubertal females: <100 ng/dL

**Adults**
- Males: <220 ng/dL
- Females
  - Follicular: <80 ng/dL
  - Luteal: <285 ng/dL
  - Postmenopausal: <51 ng/dL

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

**Clinical References:**

**FHC18 75675**

**18-Hydroxycorticosterone, Serum**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range (ng/dL)</th>
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Current as of June 14, 2021 12:13 pm CDT   800-533-1710 or 507-266-5700 or mayocliniclabs.com
Premature (26 - 28 weeks) Day 4 10 - 670
Premature (31 - 35 weeks) Day 4 57 - 410
Full-term Day 3 31 - 546
31 days to 11 months 5 - 220
12 - 23 months 18 - 155
24 months to 9 years 6 - 85
10 - 14 years 10 - 72
Adults 9 - 58
Adults 8:00 AM Supine 4 - 21
Adults 8:00 AM Upright 5 - 46

GLIOF 35272

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

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

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

Interpretation: The presence of 1p deletion and combined 1p and 19q deletion supports a diagnosis of oligodendroglioma. The presence of gain of chromosome 19 supports a diagnosis of high-grade astrocytoma (glioblastoma multiforme). A negative result does not exclude a diagnosis of oligodendroglioma or high-grade astrocytoma.

Reference Values: An interpretive report will be provided.


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

Clinical Information: Erythrocytosis (ie, increased red blood cell mass and elevated hemoglobin and hematocrit) may be primary, due to an intrinsic defect of bone marrow stem cells as in polycythemia vera (PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanism may be suspected. Unlike PV, hereditary erythrocytosis is not associated with the risk of clonal evolution and most commonly presents as isolated erythrocytosis that has been present since childhood. Hereditary erythrocytosis may be caused by alterations in one of several genes and inherited in either an autosomal dominant or autosomal recessive manner. Genetic variants causing hereditary erythrocytosis have been found in genes coding for alpha and beta hemoglobins, hemoglobin stabilization proteins (eg, 2,3-bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF, prolyl hydroxylase domain: PHD, and von Hippel Lindau: VHL), see table. High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of variants causing hereditary erythrocytosis is unknown; however, very few cases of 2,3-BPG deficiency-associated hereditary erythrocytosis have been identified and this disorder is thought to be rare. Erythrocytosis Testing Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal Normal to mildly decreased Normal Normal to increased Decreased Normal to increasedDecreased Alpha globin Dominant Normal to increased Decreased HIF2A/EPAS1 Dominant Normal to increased Normal VHL Recessive Normal to increased Normal

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

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

Reference Values: An interpretive report will be provided.

23BPG  37931  2,3-Dinor-11 Beta-Prostaglandin F2 Alpha, Urine  

**Clinical Information:** 2,3-Dinor-11beta-prostaglandin F2 alpha (2,3 BPG) is the most abundant metabolic product of prostaglandins released by activated mast cells. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase. The World Health Organization diagnostic criteria for SM require the presence of elevated mast cell counts on a bone marrow biopsy and 1 of the following minor criteria: abnormal mast cell morphology, KIT Asp816Val variant, CD25-positive mast cells, or serum tryptase greater than 20 ng/mL. Alternatively, SM diagnosis can be made with the presence of 3 minor criteria in the absence of abnormal bone marrow studies. Measurement of mast cell mediators in blood or urine is less invasive and is advised for the initial evaluation of suspected cases. Elevated levels of serum tryptase, urinary N-methylhistamine, 2,3 BPG, or leukotriene E4 are consistent with the diagnosis of systemic mast cell disease.

**Useful For:** Screening for mast cell activation disorders including systemic mastocytosis

**Interpretation:** Urinary 2,3-dinor-11beta-prostaglandin F2 alpha (2,3 BPG) values above 3263 pg/mg creatinine are consistent with, but not necessarily diagnostic of, systemic mastocytosis. Values should be interpreted in the context of clinical presentation and additional mast cell disease markers (serum tryptase, urinary N-methyl histamine, and/or urinary leukotriene E4).

**Reference Values:**

<5.205 pg/mg creatinine

**Clinical References:**


2OHGP  608030  2-Hydroxyglutaric Aciduria Gene Panel, Varies  

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

**Useful For:** Follow up for abnormal biochemical results suggestive of 2-hydroxyglutaric aciduria
Establishing a molecular diagnosis for patients with 2-hydroxyglutaric aciduria
Identifying variants within genes known to be associated with 2-hydroxyglutaric aciduria, allowing for predictive testing of at-risk family members

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**21-Deoxycortisol, Serum**

**Clinical Information:** The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions). 21-Deoxycortisol is an intermediate steroid in the glucocorticoid pathway. While the main substrate flow in glucocorticoid synthesis proceeds from 17-hydroxyprogesterone via 21-hydroxylation to 11-deoxycortisol and then, ultimately, to cortisol, a small proportion of 17-hydroxyprogesterone is also hydroxylated at carbon number 11 by 11-beta-hydroxylase 1 (CYP11B1), yielding 21-deoxycortisol. This in turn can also serve as a substrate for 21-hydroxylase (CYP21A2), resulting in formation of cortisol. The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17-alpha-hydroxylase activity). In case of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases) and those with the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies, might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases), are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone
is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, in hirsutism, polycystic ovarian syndrome or infertility, as well as in possible premature adrenarche and pubarche in both genders. Measurement of the various precursors of mature mineral corticoids and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of 21-deoxycortisol can supplement or confirm 17-hydroxyprogesterone and androstenedione measurements in the diagnosis of difficult cases of CAH presumed to be due to CYP21A2 deficiency. 11-Hydroxylation remains intact in such patients. However, since the CYP21A2 enzyme block prevents formation of 11-deoxycortisol, while simultaneously increasing the concentrations of the precursor, 17-hydroxyprogesterone, unoccupied CYP11B1 starts to 11-hydroxylate the abundant 17-hydroxyprogesterone substrate into 21-deoxycortisol. The 21-deoxycortisol accumulates, as the diminished or absent CYP21A2 activity slows or prevents its conversion into cortisol. For other forms of CAH the following tests might be relevant: -11-Hydroxylase deficiency: Â - DOC / 11-Deoxycortisol, Serum Â - CORTC / Corticosterone, Serum Â - PRA / Renin Activity, Plasma Â - ALDS / Aldosterone, Serum -3-Beta-steroid-dehydrogenase deficiency: Â - 17PRN / Pregnenolone and 17-Hydroxyprogrenolone -17-Hydoxydehydrogenase deficiency or 17-lyase deficiency (CYP17A1 has both activities): Â - PREGN / Pregnenolone, Serum Â - 17OHP / 17-Hydroxypregnenolone, Serum Â - PGSN / Progesterone, Serum Â - OHPG / 17-Hydroxyprogesterone, Serum Â - DHEA_ / Dehydroepiandrosterone (DHEA), Serum Â - ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. It has been suggested that in the pubertal patient with 21-hydroxylase deficiency, 21-deoxycortisol may be useful and better then 17-hydroxyprogesterone for therapeutic decisions.

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

Interpretation: In untreated 21-hydroxylase (CYP21A2) deficiency, 21-deoxycortisol serum concentrations on average exceed the upper limit of the reference range 30-fold to 40-fold. 21-Hydroxycortisol measurements are particularly useful in equivocal cases of suspected 21-hydroxylase deficiency. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL (upper limit of reference range for newborns) to 2,000 ng/dL or 3,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly-to-modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male).

11-Hydroxylase deficiency, in particular if it affects 11 beta-hydroxylase 1 (CYP11B1), can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases testing for CYP11B1 deficiency and 11 beta-hydroxylase 2 (CYP11B2) deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in such cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires via 11-hydroxylation of 17-hydroxyprogesterone. For genetic counseling purposes, identification of asymptomatic carriers of CYP21A2 mutations and deletions is sometimes required. The gold-standard is full DNA sequencing of CYP21A2, its pseudogene CYP21A1P, and, if possible, recombinants of gene and pseudogene, along with deletion detection. Such a procedure is costly and complex, and often has a slow turnaround time. Therefore, many laboratories perform less complex, but also less complete, mutation and deletion assessments, which may miss a significant minority of heterozygote carriers. Biochemical testing using adrenocorticotropic hormone (ACTH) ACTH1-24 adrenal stimulation represents an alternative. However, for 17-hydroxyprogesterone and androstenedione measurements there is significant overlap between poststimulation results in normals and in heterozygote carriers. By contrast, poststimulation 21-deoxycortisol concentrations of 55 ng/dL identify virtually all heterozygote carriers, with minimal overlap with normal subjects. The goal of congenital adrenal hyperplasia (CAH) treatment is normalization of cortisol levels and ideally also of sex steroid levels. Serum 17-hydroxyprogesterone, androstenedione, and testosterone should be
measured and used to guide treatment modifications. Normal prepubertal androgen levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable. 17-Hydroxyprogesterone levels should not significantly exceed the normal reference range at any time of the day. However, during puberty, the changing levels of sex steroid production may make 17-hydroxyprogesterone measurements less reliable. Since 21-deoxycortisol is not a sex-steroid precursor, its levels appear more reliable during the pubertal period, again, the aim being not to exceed the reference range significantly.

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


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

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

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

Reference Values:
Negative


21-Hydroxylase Gene (CYP21A2), Full Gene Analysis, Varies
**Clinical Information:** Congenital adrenal hyperplasia (CAH), with an incidence rate of 1 in 10,000 to 18,000 live births, is one of the most common inherited syndromes. The condition is characterized by impaired cortisol production due to inherited defects in steroid biosynthesis. The clinical consequences of CAH, besides diminished cortisol production, depend on which enzyme is affected and whether the loss of function is partial or complete. In greater than 90% of CAH cases, the affected enzyme is 21-steroid hydroxylase, encoded by the CYP21A2 gene located on chromosome 6 within the highly recombinant human histocompatibility complex locus. 21-hydroxylase deficient CAH is inherited in an autosomal recessive pattern and has a spectrum of clinical phenotypes depending upon residual enzyme activity. Excessive adrenal androgen biosynthesis results in varying degrees of virilization. If there is some residual enzyme activity, a non-classical phenotype results, with signs of hyperandrogenism typically starting in later childhood or adolescence. Individuals with severe enzyme deficiency have classical CAH, with prenatal onset of virilization. Classical CAH which is subdivided into simple-virilizing (minimal residual enzyme activity) and salt-wasting (no residual enzyme activity) forms. Patients with salt-wasting CAH have both cortisol and mineral corticosteroid deficiency and are at risk for life-threatening salt-wasting crises if untreated. Because of its high incidence rate, 21-hydroxylase deficiency is screened for in most US newborn screening programs, typically by measuring 17-hydroxyprogesterone concentrations in blood spots by immunoassay. Confirmation by other testing strategies (eg, LC-MS/MS, CAHBS / Congenital Adrenal Hyperplasia [CAH] Newborn Screening, Blood Spot), or retesting after several weeks, is required for most positive screens because of the high false-positive rates of the immunoassays (due to physiological elevations of 17-hydroxyprogesterone in premature babies and immunoassay cross-reactivity with other steroids). In a small percentage of cases, additional testing will fail to provide a definitive diagnosis. In addition, screening strategies can miss many non-classical cases, which may present later in childhood or adolescence and require more extensive steroid hormone profiling, including testing before and after adrenal stimulation with adrenocorticotropic hormone (ACTH)-1-24. For these reasons, genetic diagnosis plays an important ancillary role in both classical and non-classical cases. In addition, the high carrier frequency (approximately 1 in 50) for CYP21A2 mutations makes genetic diagnosis important for genetic counseling. Genetic testing can also play a role in prenatal diagnosis of 21-hydroxylase deficiency. However, accurate genetic diagnosis continues to be a challenge because most of the mutations arise from recombination events between CYP21A2 and its highly homologous pseudogene, CYP21A1P (transcriptionally inactive). In particular, partial or complex rearrangements (with or without accompanying gene duplication events), which lead to reciprocal exchanges between gene and pseudogene, can present severe diagnostic challenges. Comprehensive genetic testing strategies must therefore allow accurate assessment of most, or all, known rearrangements and mutations, as well as unequivocal determination of whether the observed changes are located within a potentially transcriptionally active genetic segment. Testing of additional family members is often needed for clarification of genetic test results.

**Useful For:** Carrier screening and diagnosis of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH) in individuals with a personal or family history of 21-hydroxylase deficiency, or as follow-up to positive CAH newborn screens and/or measurement of basal and adrenocorticotropic hormone- 1-24 stimulated 17-hydroxyprogesterone, androstenedione, and other adrenal steroid levels. May be used to identify CYP21A2 mutations in individuals with a suspected diagnosis of 21-hydroxylase deficient CAH when a common mutation panel is negative or only identifies 1 mutation. In prenatal cases of ambiguous genitalia detected by ultrasound, particularly when the fetus is confirmed XX female by chromosome analysis. This test ID should also be used for known/familial variant analysis for CYP21A2. Due to the complexity of the CYP21A2 locus, site specific testing for known/familial variants is not offered for this gene.

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

**Reference Values:** An interpretive report will be provided.

**Clinical References:** 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of
22q11.2 Deletion/Duplication, FISH

Clinical Information: The 22q deletion syndrome and 22q duplication syndrome have overlapping phenotypes. Deletions of 22q are associated with DiGeorge and velocardiofacial syndrome. These syndromes are manifested by the presence of growth deficiency, global developmental delay, heart defect, and hearing loss. The major birth defects include palatal clefting or insufficiency and thymus aplasia. Prominent facial features are widely spread eyes, superior placement of eyebrows, downward slanting palpebral fissures with or without ptosis (droopy upper eyelid), mild micrognathia (small jaw), and a long, narrow face. FISH studies are highly specific and do not exclude other chromosome abnormalities.

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

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

Reference Values:
An interpretive report will be provided.

Clinical References:
influencing gene transcription patterns in target organs. 25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process, regulated by PTH, might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents overproduction of DHVD and resultant vitamin D toxicity. Based on these considerations circulating 25HDN is the best indicator of optimal vitamin D body stores. The exact levels of optimal circulating 25HDN concentrations remain a matter of debate. Mild-to-modest deficiency can be associated with osteoporosis or secondary hyperparathyroidism. Severe deficiency may lead to failure to mineralize newly formed osteoid in bone, resulting in rickets in children and osteomalacia in adults. The consequences of vitamin D deficiency on organs other than bone are not fully known, but might include increased susceptibility to infections, muscular discomfort, and an increased risk of colon, breast, and prostate cancer. Modest 25HDN deficiency is common; in institutionalized elderly, its prevalence may be greater than 50%. Although much less common, severe deficiency is not rare either. Reasons for suboptimal 25HDN levels include lack of sunshine exposure, a particular problem in Northern latitudes during winter; inadequate intake; malabsorption (eg, due to celiac disease); depressed hepatic vitamin D 25-hydroxylase activity, secondary to advanced liver disease; and enzyme-inducing drugs, in particular many antiepileptic drugs, including phenytoin, phenobarbital, and carbamazepine, which increase 25HDN metabolism.

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

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

**Reference Values:**

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

- <10 ng/mL (severe deficiency)*
- 10-19 ng/mL (mild to moderate deficiency)**
- 20-50 ng/mL (optimum levels)***
- 51-80 ng/mL (increased risk of hypercalciuria)****
- >80 ng/mL (toxicity possible)*****

*Could be associated with osteomalacia or rickets
**May be associated with increased risk of osteoporosis or secondary hyperparathyroidism**

***Optimum levels in the healthy population; patients with bone disease may benefit from higher levels within this range***

****Sustained levels >50 ng/mL 25OH-VitD along with prolonged calcium supplementation may lead to hypercalciuria and decreased renal function

*****80 ng/mL is the lowest reported level associated with toxicity in patients without primary hyperparathyroidism who have normal renal function. Most patients with toxicity have levels >150 ng/mL. Patients with renal failure can have very high 25-OH-VitD levels without any signs of toxicity, as renal conversion to the active hormone 1,25-OH-VitD is impaired or absent.

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

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

**Clinical References:**

**Clinical Information:** Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols. The 25HDN / 25-Hydroxyvitamin D2 and D3, Serum assay is the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. In the presence of renal disease, DHVD / 1,25-Dihydroxyvitamin D, Serum testing might be needed to adequately assess vitamin D status. For patients with loss of function inactivating CYP24A1 mutations, this test (2425D / 25-Hydroxyvitamin D2 and D3:24,25-Dihydroxyvitamin D Ratio, Serum) may be helpful Loss of function mutations in the CYP24A1 gene have been shown to lead to insufficient deactivation of bioactive vitamin D metabolites, resulting in a phenotype characterized by suppressed serum parathyroid hormone (PTH), increased serum 1,25-dihydroxyvitamin D (DHVD) concentrations, hypercalcemia, and hypercalciuria or nephrolithiasis. Vitamin D compounds in the body are exogenously derived by dietary means; from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. 25-Hydroxyvitamin D (25HDN) is subsequently formed by hydroxylation (CYP2R1) in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD the active metabolite of 25HDN. 1-Alpha-hydroxylation (CYP27B1) occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process regulated by parathyroid hormone (PTH) might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents over production of DHVD and resultant vitamin D toxicity. DHVD stimulates
calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and PTH. DHVD promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the PTH glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, DHVD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs. DHVD levels are decreased in hypoparathyroidism and in chronic renal failure. DVHD levels may be high in primary hyperparathyroidism and in physiologic hyperparathyroidism secondary to low calcium or vitamin D intake. Some patients with granulomatous diseases (eg, sarcoidosis) and malignancies containing nonregulated 1-alpha hydroxylase in the lesion might have hypercalcemia that appears vitamin D mediated with normal or high serum phosphate (hyperphosphatemia) and hypercalcemia (both of which might be severe), in addition to low parathyroid hormone (PTH) and absent parathyroid hormone-related peptide (PTHRP). Differential diagnostic considerations include vitamin D intoxication and CYP24A1 deficiency

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

**Interpretation:** Results should be interpreted in the context of other biochemical findings including serum calcium, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D (DHVD) concentrations. If 25-hydroxyvitamin D (25HDN) result is less than 20 ng/mL, the ratio of 25-OH-D to 24,25-dihydroxyvitamin D (24,25D) will be falsely elevated since there is no inactivation of 25-OH-D to 24,25D. 24,25D formation by CYP24A1 is dependent on CYP24A1 activity and the concentrations of its substrate, 25HDN. The ratio of 25HDN to 24,25D, therefore, allows the most reliable estimation of CYP24A1 activity. Ratios of 25HDN to 24,25D less than 25 may be interpreted as normal, though ratios of 25HDN to 24,25D between 25 and 80 range may be seen in patients with low vitamin D or heterozygous CYP24A1 mutations. Ratios of 25HDN to 24,25D greater than 80 indicate probable biallelic CYP24A1 mutation or deletion. Confirmation with molecular testing is recommended.

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

25HDN to 24,25D ratio less than 25*
*Interpretation: Normal (Ratio of less than 25 may also be observed in heterozygous carriers of CYP24A1 mutations)

25HDN to 24,25D ratio between 25-80**
**Interpretation: Ratios in the 25 to 80 range can be seen in patients with low vitamin D or heterozygous CYP24A1 mutations. Confirmation with molecular testing is recommended.

25HDN to 24,25D ratio greater than 80***
***Interpretation: Ratios greater than 80 indicate probable biallelic CYP24A1 mutation or deletion. Confirmation with molecular testing is recommended.

Reference values not applicable for 24,25 Dihydroxyvitamin D Total result.

Results should be interpreted in the context of other biochemical findings including serum calcium, parathyroid hormone, and 1,25 dihydroxyvitamin D concentrations. If 25-OH-D is less than 20 ng/ml the ratio of 25-OH-D to 24,25-dihydroxyvitamin D will be falsely elevated since there is no inactivation 25-OH-D to 24,25-dihydroxyvitamin D.

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

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

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

Reference Values:<20.0 CU

3-Methoxytyramine, 24 Hour, Urine

Clinical Information: Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating (spells). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Dopamine secreting tumors are rarer than norepinephrine and epinephrine secreting tumors. 3-Methoxytyramine (3MT), metanephrine, and normetanephrine are the metabolites of dopamine, epinephrine, and norepinephrine, respectively. These metabolites are further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. This test may be used as the first test for low-suspicion cases and also as a confirmatory study in patients with less than a 2-fold elevation in plasma free fractionated catecholamines. This is highly desirable, as the very low population incidence rate of pheochromocytoma (<1:100,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures.

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

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

Reference Values:
Males: < or =306 mcg/24 hours
Females: < or =242 mcg/24 hours

Clinical References:

3-Methylglutaconic Aciduria Panel, Varies

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

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

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**F5NUL**

5’Nucleotidase

**Useful For:**

**Reference Values:**

0 - 15 U/L

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**FLUC**

5-Flucytosine, Serum

**Clinical Information:** Flucytosine is a broad-spectrum antifungal agent generally used in combined therapy (often with amphotericin B) for treatment of fungal infections such as cryptococcal meningitis. Concerns with toxicity (bone marrow suppression, hepatic dysfunction) and development of fungal resistance limit the use of flucytosine, particularly as a monotherapy. The drug is well-absorbed orally, but can also be administered intravenously (available outside of the United States). There is good correlation between serum concentrations of flucytosine with both efficacy and risk for toxicity. Because of the drugs short half-life (3-6 hours), therapeutic monitoring is typically performed at peak levels, 1 to 2 hours after an oral dose or 30 minutes after an intravenous administration. Flucytosine is eliminated primarily as unmetabolized drug in urine. Patients with renal dysfunction may require dose adjustments or more frequent monitoring to ensure that serum concentrations do not accumulate to excessive levels. Nephrotoxicity associated with use of amphotericin B can affect elimination of flucytosine when the drugs are coadministered.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity May be useful to evaluate patient compliance

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

**Reference Values:**

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


FHIAA 75515
5-HIAA (5-Hydroxyindoleacetic acid), Plasma

Clinical Information: The ISI plasma 5-HIAA assay correlates well with the 24-hour urinary 5-HIAA assays. This test has been clinically validated for NETS patients who previously relied on the 24-hour urinary 5-HIAA. The plasma 5-HIAA saves time, alleviates the need to collect urine in a container for 24 hours, and provides equivalent clinical information.

Reference Values:
Up to 22 ng/mL


F5HAR 57333
5-Hydroxyindoleacetic Acid (5-HIAA), Random Urine with Creatinine

Reference Values:
5-HIAA mg/g creat
2-10 YRS: 12.0 or less
>10 YRS: 10.0 or less

Creatinine, Random Urine mg/dL
Age
0-6 Months 2-32
7-11 Months 2-36
1-2 Years 2-128
3-8 Years 2-149
9-12 Years 2-183
>12 Years
Males: 20-370
Females: 20-320

HIAA 9248
5-Hydroxyindoleacetic Acid, 24 Hour, Urine

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

**Useful For:** Biochemical diagnosis and monitoring of intestinal carcinoid syndrome

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

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

**Clinical References:**
5-Methyltetrahydrofolate

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

Reference Values:
5-Methyltetrahydrofolate

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5MTHF (nmol/L)</th>
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</thead>
<tbody>
<tr>
<td>0-0.2</td>
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<td>Adults</td>
<td>40-120</td>
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</table>

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

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

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

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

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

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

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentration:
6-MAM by LC-MS/MS: 5 ng/g

Clinical References:

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

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

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

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

Reference Values:
- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentration:
  - 6-MAM by LC-MS/MS: 5 ng/g


6MAMU

6-Monoacetylmorphine Confirmation, Random, Urine

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though elsewhere it is used for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin.(2,3) Heroin is rarely found intact in urine, since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window.

Useful For: Determination of heroin use

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

Reference Values:
6-Monoacetylmorphine, Chain of Custody, Random, Urine

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though elsewhere it is used for rapid relief of pain. Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system. Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin. Heroin is rarely found intact in urine, since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. This includes a record of the disposition of a specimen to document the personnel who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Determination of heroin use in urine specimens handled through the chain-of-custody process

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

Reference Values:
Negative
Cutoff concentrations:
6-MAM
<5 ng/mL

68kD (hsp-70)

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

**Reference Values:**
Qualitative test – Positive or Negative

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7AC4, Bile Acid Synthesis, Serum

**Clinical Information:** Bile acids are synthesized from cholesterol in the liver and released into the digestive tract where they function to emulsify dietary fats and facilitate lipid absorption in the small intestine. More than 95% of bile acids are then reabsorbed primarily by active uptake in the distal ileum, while less than 5% are excreted in stool. The synthesis of bile acids in the liver is regulated by a negative feedback mechanism from the bile acids reabsorbed from the intestine. 7 Alpha-hydroxy-4-cholesten-3-one (7αC4) is an intermediate in the biosynthesis pathway of cholesterol to bile acids. The concentration of 7αC4 in serum is a surrogate for the amount of bile acid synthesis in the liver. There is some diurnal variation in 7αC4 serum concentrations, so measurement should be performed on a fasting morning sample. Patients with increased bile acid in their stool suffer from chronic diarrhea termed bile acid diarrhea (BAD). Approximately 10% to 33% of patients with irritable bowel syndrome with primarily diarrhea (IBS-D) have BAD. Identifying patients with BAD can be done by measuring total and fractionated bile acids in stool. The increased bile acids in feces can be caused by an inability to reabsorb bile acids in the terminal ileum (bile acid malabsorption: BAM). The loss of intestinal reabsorption leads to increased synthesis of bile acids in the liver. Recent studies have shown that serum concentrations of 7αC4 are elevated in patients with BAD and can be used as a surrogate to the timed fecal collection. Several intestinal diseases or functional abnormalities can lead to BAD. Identification of these patients can influence treatment decisions that could include the use of bile acid sequestrants. Conversely, patients with IBS with predominately constipation (IBS-C) may have lower circulating 7αC4 as compared to healthy individuals.

**Useful For:** Screening for bile acid malabsorption in patients with irritable bowel syndrome-diarrhea (IBS-D)

**Interpretation:** In patients with irritable bowel syndrome-diarrhea (IBS-D), elevated 7alpha-hydroxy-4-cholesten-3-one (7αC4) is consistent with bile acid diarrhea (BAD). A result of 17.6 ng/mL or greater is 83% sensitive and 53% specific for BAD. In these cases, a confirmatory 48-hour fecal bile acid test could be considered. A result above 52.5 ng/mL is 40% sensitive and 85% specific for BAD. Interpretation in patients with chronic diarrhea (bile acid malabsorption: BAM):

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-- BAM unlikely
Indeterminate BAM likely (consider other (consider confirmatory (consider bile acid conditions) fecal bile acids test or trial sequestrant therapy) of bile acid sequestrant)

**Reference Values:**

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

**Clinical References:**
**A1R**

**A1 Antigen Subtype, Whole Blood**

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

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

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

**Reference Values:**
Reported as Negative or Positive


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**G111**

**Abnormal Transferrin CDG Panel (Bill Only)**

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

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**ABONR**

**ABO/Rh Newborn, RBC**

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

**Useful For:** Selecting compatible blood products for transfusion therapy Determining the need for Rh immune globulin in mother of baby

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

**Reference Values:**
ABO and Rh blood group antigens identified


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**ABOMR**

**ABO/Rh, RBC**

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

**Useful For:** Determining blood group ABO and Rh only

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

**Reference Values:**

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Acacia, IgE, Serum

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

Useful For: Establishing the diagnosis of an allergy to acacia Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages</td>
</tr>
</tbody>
</table>

environment, many people will be exposed to Acanthamoeba during their lifetime, but very few will become sick from this exposure. The most common form of Acanthamoeba infection is amebic keratitis (AK). Infection occurs primarily in contact lens wearers due to contamination of lenses, cleaning solutions, or storage cases. Amebae can also enter the cornea following trauma. AK is a painful, subacute corneal infection associated with extensive scarring and blindness if untreated. Cases generally respond to treatment but relapse is common. Compared to corneal infection, involvement of the CNS is rare and seen primarily in severely immunocompromised individuals such as organ transplant recipients and patients with AIDS. CNS infection may also be caused by a related ameba, Balamuthia mandrillaris. AK is usually clinically suspected based on symptoms and confocal ophthalmologic examination. Confirmation of infection is classically identified by microscopic examination and culture of corneal tissue and contact lenses or equipment using tap water agar plate overlain with bacteria as a food source for the amebae. Unfortunately, it must be held and examined for 7 days for maximum sensitivity. A polymerase chain reaction assay provides a more rapid result with similar sensitivity to culture and is, therefore, the preferred method for confirming the clinical diagnosis of AK.

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

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

**Reference Values:**
- Negative

**Clinical References:**

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**ACAR**

**82850**

**Acarus siro, IgE, Serum**

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

**Useful For:** Establishing the diagnosis of an allergy to Acarus siro (flour mites) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
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</table>
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FACET 57707  Acetaminophen (Tylenol, Datril), Urine
Reference Values:
Units: ug/mL
Note: Analysis performed on urine.
Reference ranges have not been established for urine specimens.

ACMA 37030  Acetaminophen, Serum
Clinical Information: Acetaminophen (found in Anacin-3, Comtrex, Contac, Datril, Dristan, Excedrin, Nyquil, Sinutab, Tempera, Tylenol, Vanquish, and many others) is an analgesic, antipyretic drug lacking significant anti-inflammatory activity. It is metabolized by the liver with a normal elimination half-life of less than 4 hours. In normal therapeutic doses, a minor metabolite, possessing electrophilic alkylating activity, readily reacts with glutathione in the liver to yield a detoxified product. In overdose situations, liver glutathione is consumed and the toxic metabolite (postulated metabolite: benzoquinone) reacts with cellular proteins resulting in hepatotoxicity, characterized by centrilobular necrosis and possible death if untreated. N-acetylcysteine can substitute for glutathione and serves as an antidote. Serum concentration and half-life are the only way to assess degree of intoxication in early stages since other liver function studies (eg, bilirubin, liver function enzymes) will not show clinically significant increases until after tissue damage has occurred, at which point therapy is ineffective.

Useful For: Monitoring toxicity in overdose cases

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


FACES 75388  Acetoacetate, Serum
Reference Values:
Reporting limit determined each analysis.

Acetoacetate
Normal range for adults: 5-30 mcg/mL
Acetylcholine Receptor (Muscle AChR) Binding Antibody, Serum

Clinical Information: Myasthenia gravis (MG) is characterized by weakness and easy fatigability that are relieved by rest and anticholinesterase drugs. The weakness in most cases results from an autoimmune-mediated loss of functional acetylcholine receptors (AChR) in the postsynaptic membrane of skeletal muscle. Demonstration of muscle AChR autoantibodies in a patient's serum supports the diagnosis of acquired (autoimmune) MG, and quantitation provides a baseline for future comparisons. Muscle AChR antibodies are not found in congenital forms of MG and are uncommon in neurologic conditions other than acquired MG, with the exception of patients with paraneoplastic autoimmune neurological disorders, and Lambert-Eaton myasthenic syndrome (LES) with or without cancer (13% of LES patients have positive results for muscle AChR binding or striational antibodies). Patients with autoimmune liver disease are also frequently seropositive. The assay for muscle AChR binding antibodies is considered a first-order test for the laboratory diagnosis of MG, and for detecting "subclinical MG" in recipients of D-penicillamine, in patients with thymoma without clinical evidence of MG, and in patients with graft-versus-host disease.

Useful For: A first-order test for the laboratory diagnosis of myasthenia gravis (MG) Detecting "subclinical MG" in recipients of D-penicillamine, in patients with thymoma without clinical evidence of MG, and in patients with graft-versus-host disease Distinguishing acquired disease (90% positive) from congenital disease (negative) Monitoring disease progression in MG or response to immunotherapy An adjunct to the test for P/Q-type calcium channel binding antibodies as a diagnostic aid for Lambert-Eaton myasthenic syndrome (LES) or primary lung carcinoma

Interpretation: Values above 0.02 nmol/L are consistent with a diagnosis of acquired myasthenia gravis (MG), provided that clinical and electrophysiological criteria support that diagnosis. The assay for muscle acetylcholine receptor (AChR) binding antibodies is positive in approximately 90% of non-immunosuppressed patients with generalized MG. The frequency of antibody detection is lower in MG patients with weakness clinically restricted to ocular muscles (71%), and antibody titers are generally low in ocular MG (eg, 0.03-1.0 nmol/L). Results may be negative in the first 12 months after symptoms of MG appear or during immunosuppressant therapy. Note: In follow up of seronegative patients with adult-acquired generalized MG, 17.4% seroconvert to positive at 12 months (ie, seronegativity rate at 12 months is 8.4%). Of persistently seronegative patients, 38% have muscle-specific kinase (MuSK) antibody. Sera of nonmyasthenic subjects bind 0.02 nmol/L or less of muscle AChR complexed with (125)I-labeled-alpha-bungarotoxin. In general, there is not a close correlation between antibody titer and severity of weakness, but in individual patients, clinical improvement is usually accompanied by a decrease in titer.

Reference Values:
< or =0.02 nmol/L


Acetylcholine Receptor Modulating Antibody, Flow Cytometry Assay, Serum

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

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

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

**Reference Values:**
Only orderable as part of a profile. For more information see:
- MGLE / Myasthenia Gravis (MG)/Lambert-Eaton Myasthenic Syndrome (LEMS) Evaluation, Serum
- MGMR / Myasthenia Gravis Evaluation with MuSK Reflex, Serum
- PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum

**Clinical References:**

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**Acetylcholinesterase, Amniotic Fluid**

**Clinical Information:** Neural tube defects (NTD) are a type of birth defect involving openings along the brain and spine. They develop in the early embryonic period when the neural tube fails to completely close. NTD can vary widely in severity. Anencephaly represents the most severe type of NTD, which occurs when the cranial end fails to develop properly, resulting in an absence of the forebrain, the area of the skull that covers the brain, and the skin. Most infants with anencephaly are stillborn or die shortly after birth. NTD along the spine are referred to as spina bifida. Individuals with spina bifida may experience hydrocephalus, urinary and bowel dysfunction, club foot, lower body weakness, and loss of feeling or paralysis. Severity varies depending upon whether the NTD is covered by skin, whether herniation of the meninges and spinal cord are present, and the location of the lesion. NTD not covered by skin are referred to as open NTD and are typically more severe than closed NTD. Likewise those presenting with herniation and higher on the spinal column are typically more severe. Most NTD occur as isolated birth defects with an incidence of approximately 1 to 2 in 1,000 live births in the United States. Rates vary by geographic region with lower rates being observed in the North and West than the South and East. A fetus is at higher risk when the pregnancy is complicated by maternal conditions.
diabetes, exposed to certain anticonvulsants, or there is a family history of NTD. Studies have shown a dramatic decrease in risk as a result of maternal dietary supplementation with folic acid. The March of Dimes currently recommends that all women of childbearing age take 400 mcg of folic acid daily, increasing the amount to 600 mcg/day during pregnancy. For women who have had a prior pregnancy affected by an NTD, the recommended dose is at least 4000 mcg/day starting at least 1 month preconception and continuing through the first trimester. When an NTD is suspected based upon maternal serum alpha-fetoprotein (AFP) screening results or diagnosed via ultrasound, analysis of AFP and acetylcholinesterase (AChE) in amniotic fluid are useful diagnostic tools. AChE is primarily active in the central nervous system with small amounts of enzyme found in erythrocytes, skeletal muscle, and fetal serum. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of an open NTD.

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

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

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

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

**Clinical References:**

**Acetylcholinesterase, Erythrocytes**

**Clinical Information:** Erythrocyte acetylcholinesterase (AChE) activity is measured to evaluate possible exposure to organophosphate insecticides. Organophosphates act by irreversible inhibition of AChE. Inhibition of AChE in humans causes a variety of acute symptoms including dizziness, nausea, difficulty breathing, and even death. The presence and severity of these symptoms depend, in part, on the degree of AChE depression. Occupational pesticide handlers are at an elevated risk for exposure to these chemicals through skin contact, inhalation, or accidental ingestion. Organophosphate intoxication can be a result of one or more high exposure events or through chronic lower-level exposure. Both serum and erythrocyte cholinesterase activity are inhibited by these insecticides, which are among the most commonly used pesticides in the United States. The half-life of serum cholinesterase (eg, pseudocholinesterase) is about 8 days, while the half-life of AChE in erythrocytes is between 2 and 3 months. Therefore, erythrocyte AChE is an indicator of chronic and temporally distant exposures to organophosphates.

**Useful For:** Detecting effects of chronic or remote (months) past exposure to cholinesterase inhibitors (organophosphate insecticide poisoning)

**Interpretation:** Activities less than normal are suspect for exposure to certain insecticides. For occupational high-risk individuals, a pre-exposure "baseline" is recommended.

**Reference Values:**
31.2-61.3 U/g of hemoglobin

**Clinical References:**

**ASCL1**

**Achaete-Scute Homolog 1 Immunostain, Technical Component Only**

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

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

**Interpretation:** This test does not include pathologist interpretation only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**GAAWR**

**Acid Alpha-Glucosidase Reflex, Leukocytes**

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

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

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

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

> or =1.50 nmol/hour/mg protein

**Clinical References:**

GAAW 606267

**Acid Alpha-Glucosidase, Leukocytes**

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

**Useful For:** Diagnosis of Pompe disease

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

**Reference Values:**
> or = 1.50 nmol/hour/mg protein

An interpretive report is provided.

**Clinical References:**

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**ASMW 606264**

**Acid Sphingomyelinase, Leukocytes**

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

**Useful For:** Investigation of possible diagnosis of Niemann-Pick disease types A and B. This test is not recommended for carrier detection because of the wide range of enzymatic activities observed in carriers and noncarriers.
**Interpretation:** Values below the reference range are consistent with a diagnosis for Niemann-Pick types A and B. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

\[ \geq 0.32 \text{ nmol/hour/mg protein} \]

An interpretative report will be provided.

**Clinical References:**

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

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

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Actinomyces Culture, Varies**

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

**Useful For:** Diagnosing anaerobic Actinomyces involved in infections

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

**Reference Values:**
No growth
Identification of probable pathogens

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

Clinical Information: The activated partial thromboplastin time (APTT) mix is only performed when the APTT is abnormally prolonged. Refer to APTS / Activated Partial Thromboplastin Time (APTT), Plasma for interpretation of results. The APTT mixing test is used to evaluate a prolonged APTT test result, especially when mixing test results are combined with results of other coagulation tests and clinical information, to assist in differentiating coagulation factor deficiencies from coagulation inhibitors.

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

Interpretation: Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. The APTT mixing study, using equal volumes of patient and normal pool plasma, may be performed on specimens with a prolonged APTT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors of all types (1-4). Correction of the APTT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged APTT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the APTT mix typically fails to correct a prolonged APTT. However, the presence of a weak inhibitor may be missed by the APTT mixing study. Accurate interpretation of both APTT and APTT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the prothrombin time (PT) and dilute Russell viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, APROL / Prolonged Clot Time Profile, Plasma). Shortening of the APTT usually reflects either elevation of factor VIII activity secondary to acute or chronic illness or inflammation, or spurious results from suboptimal venipuncture, specimen collection or processing. A normal or shortened APTT result does not exclude a hemostatic defect; and specific clotting factor assays should be performed despite a normal APTT when there is clinical impression of bleeding diathesis.

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

25-37 seconds

Activated Partial Thromboplastin Time (APTT), Plasma

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

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

Interpretation: Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. The APTT mixing study, which uses equal volumes of patient and normal pool plasma, may be performed on specimens with a prolonged APTT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors of all types.(1-4) Correction of the APTT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged APTT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the APTT mix typically fails to correct a prolonged APTT. However, the presence of a weak inhibitor may be missed by the APTT mixing study. Accurate interpretation of both APTT and APTT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the prothrombin time (PT) and dilute Russell's viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, APROL / Prolonged Clot Time Profile). The APTT test is frequently used to monitor therapy with unfractionated heparin (UFH). Since
APTTP reagents can vary greatly in their sensitivity to UFH, it is important to establish a relationship between APTT response and heparin concentration. The therapeutic APTT range in seconds should correspond with a UFH concentration of 0.3 to 0.7 U/mL as assessed by a heparin assay (inhibition of factor Xa activity with detection by a chromogenic substrate [1]). We have established the therapeutic APTT range to be approximately 70 to 120 seconds. Shortening of the APTT usually reflects either elevation of factor VIII activity secondary to acute or chronic illness or inflammation, or spurious results from suboptimal venipuncture, specimen collection or processing. A normal or shortened APTT result does not exclude a hemostatic defect; and specific clotting factor assays should be performed despite a normal APTT when there is clinical impression of bleeding diathesis.

**Reference Values:**

Only orderable as part of a special coagulation profile or as a reflex. For more information see:

- ALUPP / Lupus Anticoagulant Profile, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- AATHR / Thrombophilia Profile, Plasma
- APROL / Prolonged Clot Time Profile, Plasma
- ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

25–37 seconds

The APTT may be 35% longer in full-term newborns that reach adult reference range by age 3 months and twice the adult upper limit in premature infants reaching adult reference range by age 6 months.

**Clinical References:**


**Activated Partial Thromboplastin Time, Plasma (40935)**

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

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

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

**Reference Values:**

25–37 seconds

**Clinical References:** 1. Clinical and Laboratory Standards Institute (CLSI). One-stage PT and APTT
Activated Protein C Resistance V (APCRV), Plasma

Clinical Information: Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight=62,000 da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa and VIIIa/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time clotting test fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have a specific point mutation in the procoagulant factor V gene (1691G-A, factor V Leiden) encoding for a glutamine (Q) substitution for arginine (R)-506 in the heavy chain of factor V (factor V R506Q). This amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden mutation varies depending on the population. Approximately 5% of asymptomatic white Americans of non-Hispanic ancestry are heterozygous carriers, while the carrier frequency among African Americans, Asian Americans, and Native Americans is less than 1%, and the carrier frequency for Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among whites of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common, but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden mutation; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

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

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

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

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

**Clinical Information:** Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight=62,000 da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC interacts with and proteolyses factors V/Va and VIII/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time clotting test fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have a specific point mutation in the procoagulant factor V gene (1691G>A, factor V Leiden) encoding for a glutamine (Q) substitution for arginine (R)-506 in the heavy chain of factor V (factor V R506Q). This amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden mutation varies depending on the population. Approximately 5% of asymptomatic white Americans of non-Hispanic ancestry are heterozygous carriers, while the carrier frequency among African Americans, Asian Americans, and Native Americans is less than 1%, and the carrier frequency for Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among whites of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common, but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden mutation; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

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

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

**Reference Values:**

APCRV RATIO

> or = 2.3

Pediatric reference range has neither been established nor is available in scientific literature. The adult reference range likely would be applicable to children older than 6 months.

**Clinical References:**

**Clinical Information:** Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of the viral hepatitis in United States adults. HAV infection is spread by the oral/fecal route and produces acute hepatitis, which follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and in institutions or high-density centers such as prisons and health care centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these chronic carriers are asymptomatic; others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. The following algorithms are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Viral Hepatitis Serologic Profiles

**Useful For:** Differential diagnosis of recent acute viral hepatitis

**Interpretation:** Hepatitis A: Antibody against hepatitis A antigen is usually detectable by the onset of symptoms (usually 15-45 days after exposure). The initial antibody consists almost entirely of IgM subclass antibody. Antibody to hepatitis A virus (anti-HAV) IgM usually falls to undetectable levels 3 to 6 months after infection. Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Initially, hepatitis B core antibody (anti-HBc) consists almost entirely of the IgM subclass. Anti-HBc, IgM can be detected shortly after the onset of symptoms and is usually present for 6 months. Anti-HBc may be the only marker of a recent HBV infection detectable following the disappearance of HBsAg, and prior to the appearance of anti-HBs, ie, window period. Hepatitis C: Hepatitis C antibody is usually not detectable during the early months following infection and is almost always detectable by the late convalescent stage of infection. Hepatitis C antibody is not neutralizing and does not provide immunity. If HBsAg, anti-HAV (IgM), and anti-HCV are negative and patient’s condition warrants, consider testing for Epstein-Barr virus or cytomegalovirus. The following algorithms are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis

**Reference Values:**

**HEPATITIS B SURFACE ANTIGEN**
Negative

**HEPATITIS B SURFACE ANTIGEN CONFIRMATION**
Negative

**HEPATITIS B CORE IgM ANTIBODY**
Negative

**HEPATITIS A IgM ANTIBODY**
Negative

**HEPATITIS C ANTIBODY**
Negative
HEPATITIS C VIRUS RNA DETECTION and QUANTIFICATION by REAL-TIME RT-PCR

Undetected

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.


**COGMF** 113528

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

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias, with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia and accounts for the majority of infant (<1 year old) leukemia. Several recurrent chromosomal abnormalities have been identified in AML. The most common chromosome abnormalities associated with AML include t(8;21), t(15;17), inv(16), and abnormalities of the MLL (KMT2A) gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML include MLLT4- t(6;11), MLLT3- t(9;11), MLLT10- t(10;11), and ELL- t(11;19p13.1). AML can also evolve from myelodysplasia (MDS). Thus, the common chromosome abnormalities associated with MDS can also be identified in AML, which include: inv(3), -5/5q-, -7/7q-, and 17p. Overall, the recurrent chromosome abnormalities identified in patients with AML are observed in approximately 60% of diagnostic AML cases.

Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in AML. However, some of the subtle rearrangements can be missed by karyotype, including inv(16) and MLL rearrangements. Fluorescence in situ hybridization (FISH) analysis of nonproliferating (interphase) cells can be used to detect the common chromosome abnormalities observed in patients with AML. The abnormalities have diagnostic and prognostic relevance, and FISH testing can also be used to track response to therapy. Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome analysis (ie, t(12;21) associated with ETV6/RUNX1 fusion) is performed as required by Children's Oncology Group (COG) and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intrachromosomal amplification of chromosome 21 (iAMP21).

Useful For: Evaluation of pediatric bone marrow and peripheral blood specimens by fluorescence in situ hybridization (FISH) probe analysis for classic rearrangements and chromosomal copy number changes associated with acute myeloid leukemia (AML) in patients being considered for enrolment in
Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an acute myeloid leukemia of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.


Acute Myeloid Leukemia (AML), FISH, Varies

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

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with acute myeloid leukemia or other myeloid malignancies Evaluating specimens in which standard cytogenetic analysis is unsuccessful Identifying and tracking known chromosome abnormalities in patients with myeloid malignancies and tracking response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an acute myeloid leukemia of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Acute Porphyria Gene Panel, Varies

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

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

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

Reference Values: An interpretive report will be provided.

for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which can be measured by tandem mass spectrometry (MS/MS). Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor and vitamin supplementation. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. The following disorders are detectable by acylcarnitine analysis. However, further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than one condition. Fatty Acid Oxidation Disorders: -Carnitine palmitoyltransferase I (CPTI) deficiency -Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency -Dienoyl-CoA reductase deficiency -Short-chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency -Carnitine palmitoyl transferase type II (CPT-II) deficiency -Carnitine-acylcarnitine translocase (CACT) deficiency -Electron transfer flavoprotein (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency [MADD]; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic acidemia -Methylmalonic acidemia -Isovaleric acidemia -3-hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -Beta-ketothiolase deficiency -Malonic aciduria -Ethylmalonic encephalopathy -Glutamate formiminotransferase deficiency (formiminoglutamic aciduria)

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

**Interpretation:** An interpretive report is provided. The individual quantitative results support the interpretation of the acylcarnitine profile but are not diagnostic by themselves. The interpretation is based on pattern recognition. Abnormal results are typically not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical or molecular genetic analyses are required. For information on the follow-up of specific acylcarnitine elevations, see Special Instructions for the following algorithms: -Newborn Screening Follow-up for Elevations of C8, C6, and C10 Acylcarnitines (also applies to any plasma or serum C8, C6, and C10 acylcarnitine elevations) -Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevation) -Newborn Screening Follow-up for Isolated C5 Acylcarnitine Elevations (also applies to any plasma or serum C5 acylcarnitine elevation)

**Reference Values:**

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Iso-/Butyrylcarnitine, C4
Tiglylcarnitine, C5:1
Isovaleryl-/2-Methylbutyrylcarn C5
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Hexenoylcarnitine, C6:1
Hexanoylcarnitine, C6
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Benzoylcarnitine
Heptanoylcarnitine, C7
3-OH-hexanoylcarnitine, C6-OH
Phenylacetylcarntine
Salicylcarnitine
Octenoylcarnitine, C8:1
Octanoylcarnitine, C8
Malonylcarnitine, C3-DC
Decadienoylcarnitine, C10:2
Decenoylcarnitine, C10:1
Decanoylcarnitine, C10
Methylmalonyl-/succinylcarn, C4-DC
3-OH-decenoylcarnitine, C10:1-OH
Glutarylcarntine, C5-DC
Dodecenoylcarnitine, C12:1
Dodecanoylcarnitine, C12
3-Methylglutarylcarntine, C6-DC
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3-OH-dodecanoylcarnitine, C12-OH
Tetradecadienoylcarnitine, C14:2
Tetradecenoylcarnitine, C14:1
Tetradecanoylcarntine, C14
Octanediylcarntine, C8-DC
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Hexadecenoylcarnitine, C16:1
Hexadecanoylcarntine, C16
3-OH-hexadecenoylcarntine, C16:1-OH
3-OH-hexadecanoylcarntine, C16-OH
Octadecadienoylcarnitine, C18:2
Octadecenoylcarnitine, C18:1
Octadecanoylcarnitine, C18
Dodecanedioylcarnitine, C12-DC
3-OH-octadecadienoylcarn, C18:2-OH
3-OH-octadecenoylcarnitine C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH

aciduria)

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

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

- Newborn Screening Follow-up for Elevations of C8, C6, and C10 Acylcarnitines (also applies to any plasma or serum C8, C6, and C10 acylcarnitine elevations)
- Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevation)
- Newborn Screening Follow-up for Isolated C5 Acylcarnitine Elevations (also applies to any plasma or serum C5 acylcarnitine elevation)

**Reference Values:**

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Dodecanoylcarnitine, C12
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3-OH-dodecanoylcarnitine, C12-OH
Tetradecadienoylcarnitine, C14:2
Tetradecenoylcarnitine, C14:1
Tetradecanoylcarnitine, C14
Octanediol carnitine, C8-DC
3-OH-tetradecenoylcarnitine C14:1-OH
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Hexadecenoylcarnitine, C16:1
Hexadecanoylcarnitine, C16
3-OH-hexadecenoylcarnitine, C16:1-OH
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Octadecadienoylcarnitine, C18:2
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Octadecanoylcarnitine, C18
Dodecanedioyl carnitine, C12-DC
3-OH-octadecadienoylcarn, C18:2-OH
3-OH-octadecenoylcarnitine C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH


Acylglycines, Quantitative, Random, Urine

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

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

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

**Reference Values:**

Reference Values; Expressed as mg/g creatinine

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<td>0.01-0.04</td>
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<td>1.33-8.05</td>
<td>1.23-7.72</td>
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<tr>
<td>n-Butyrylglycine</td>
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<td>0.17-0.84</td>
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<td>0.09-0.96</td>
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<td>0.37-3.88</td>
<td>0.38-4.28</td>
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<td>0.26-2.31</td>
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<td>0.26-2.27</td>
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Current as of June 14, 2021 12:13 pm CDT
| **Glutaric acid** | 0.34-2.39 | 0.34-1.83 | 0.35-2.29 | 0.35-2.00 | 0.35-1.97 | 0.35-1.59 |
| **3-Methylcrotonylglycine** | 0.24-0.85 | 0.24-0.85 | 0.25-0.84 | 0.25-0.83 | 0.26-0.83 | 0.26-0.83 |
| **n-Tiglylglycine** | 0.83-2.98 | 0.83-2.98 | 0.85-2.90 | 0.85-2.90 | 0.87-2.83 | 0.87-2.83 |
| **3-Methylglutaconic acid** | 1.93-7.19 | 1.93-7.19 | 1.99-7.15 | 1.99-7.15 | 2.07-7.11 | 2.07-7.11 |
| **n-Hexanoylglycine** | 0.26-1.34 | 0.26-1.31 | 0.26-1.35 | 0.26-1.35 | 0.26-1.35 | 0.26-1.35 |
| **n-Octanoylglycine** | 0.15-1.35 | 0.15-1.35 | 0.15-1.35 | 0.15-1.35 | 0.15-1.35 | 0.15-1.35 |
| **3-Phenylpropionylglycine** | 0.09-0.95 | 0.10-0.93 | 0.09-0.95 | 0.11-0.92 | 0.09-0.95 | 0.11-0.91 |
| **trans-Cinnamoylglycine** | 0.38-4.24 | 0.38-4.19 | 0.38-4.16 | 0.38-4.16 | 0.38-4.16 | 0.38-4.16 |
| **Suberylglycine** | 0.26-2.26 | 0.26-2.26 | 0.26-2.26 | 0.26-2.26 | 0.26-2.26 | 0.26-2.26 |
| **Dodecanedioic acid** | 0.01-0.06 | 0.01-0.06 | 0.01-0.06 | 0.01-0.06 | 0.01-0.06 | 0.01-0.06 |
| **Tetradecanedioic acid** | 0.01-0.04 | 0.01-0.04 | 0.01-0.04 | 0.01-0.04 | 0.01-0.04 | 0.01-0.04 |
| **Hexadecanedioic acid** | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 |

| **n-Acetylglycine** | 0.15-0.80 | 0.15-0.80 | 0.15-0.79 | 0.15-0.79 | 0.15-0.78 | 0.15-0.78 |
| **n-Propionylglycine** | 0.16-0.66 | 0.16-0.66 | 0.16-0.65 | 0.16-0.65 | 0.17-0.64 | 0.17-0.64 |
| **Isobutyrylglycine** | 0.19-1.69 | 0.20-1.70 | 0.19-1.68 | 0.21-1.66 | 0.19-1.66 | 0.22-1.62 |
| **Ethylmalonic acid** | 1.33-6.92 | 1.23-6.92 | 1.33-6.84 | 1.24-6.80 | 1.34-6.78 | 1.25-6.41 |
| **n-Butyrylglycine** | 0.20-0.92 | 0.20-0.92 | 0.20-0.91 | 0.20-0.91 | 0.20-0.90 | 0.20-0.90 |
| **2-Methylsuccinic acid** | 0.54-2.62 | 0.54-2.62 | 0.54-2.58 | 0.54-2.48 | 0.54-2.62 | 0.54-2.62 |
| **2-Methylbutyrylglycine** | 0.10-0.87 | 0.10-0.87 | 0.10-0.87 | 0.10-0.86 | 0.10-0.86 | 0.10-0.86 |
| **Isovalerylglycine** | 0.54-4.49 | 0.54-4.49 | 0.55-4.37 | 0.55-4.37 | 0.56-4.26 | 0.56-4.26 |
| **Glutaric acid** | 0.35-2.13 | 0.35-2.13 | 0.35-2.06 | 0.36-2.06 | 0.35-2.06 | 0.36-2.06 |
| **3-Methylcrotonylglycine** | 0.28-0.83 | 0.28-0.83 | 0.29-0.82 | 0.29-0.82 | 0.30-0.82 | 0.30-0.82 |
| **n-Tiglylglycine** | 0.90-2.76 | 0.90-2.76 | 0.93-2.70 | 0.93-2.70 | 0.95-2.64 | 0.95-2.64 |
| **3-Methylglutaconic acid** | 2.17-7.07 | 2.17-7.07 | 2.29-7.02 | 2.29-7.02 | 2.41-6.95 | 2.41-6.95 |
| **n-Hexanoylglycine** | 0.26-1.29 | 0.26-1.29 | 0.26-1.27 | 0.29-1.00 | 0.26-1.26 | 0.29-0.98 |
| **n-Octanoylglycine** | 0.15-1.33 | 0.15-1.33 | 0.16-1.32 | 0.16-1.32 | 0.16-1.30 | 0.16-1.30 |
| **3-Phenylpropionylglycine** | 0.10-0.94 | 0.11-0.89 | 0.10-0.94 | 0.12-0.88 | 0.10-0.94 | 0.12-0.87 |
| **trans-Cinnamoylglycine** | 0.38-4.13 | 0.38-4.13 | 0.39-4.10 | 0.36-3.02 | 0.39-4.08 | 0.37-2.89 |
| **Suberylglycine** | 0.26-2.21 | 0.26-2.21 | 0.26-2.19 | 0.26-2.19 | 0.26-2.19 | 0.26-2.19 |
| **Dodecanedioic acid** | 0.01-0.06 | 0.01-0.06 | 0.01-0.05 | 0.01-0.05 | 0.01-0.05 | 0.01-0.05 |
| **Tetradecanedioic acid** | 0.01-0.03 | 0.01-0.03 | 0.01-0.03 | 0.01-0.03 | 0.01-0.03 | 0.01-0.03 |
| **Hexadecanedioic acid** | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 | 0.01-0.02 |

<p>| Current as of June 14, 2021 12:13 pm CDT | 800-533-1710 or 507-266-5700 or mayocliniclabs.com | Page 76 |</p>
<table>
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<tr>
<th>Compound</th>
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<th>Male 14-26 Years</th>
<th>Female 27-49 Years</th>
<th>Male 27-49 Years</th>
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<td>0.23-1.48</td>
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<tr>
<td>Ethylmalonic acid</td>
<td>1.35-6.74</td>
<td>1.25-6.04</td>
<td>1.36-6.72</td>
<td>1.26-5.69</td>
<td>1.37-6.70</td>
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<tr>
<td>n-Butyrylglycine</td>
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<td>0.20-0.71</td>
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<td>2-Methylsuccinic acid</td>
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<td>0.55-2.32</td>
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<td>0.31-0.81</td>
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27 Years  28 Years  29 Years

Female Male   Female Male   Female Male   Male
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**30 Years**

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<tbody>
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<td><strong>n-Acetylglycine</strong></td>
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<td>0.15-0.64</td>
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<td>0.16-0.62</td>
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<td>1.42-6.54</td>
<td>1.43-6.48</td>
<td>1.42-6.48</td>
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<td><strong>n-Butyrylglycine</strong></td>
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<td>0.21-0.81</td>
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<td><strong>2-Methylsuccinic acid</strong></td>
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<td>0.60-2.50</td>
<td>0.60-2.50</td>
<td>0.61-2.47</td>
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**33 Years**

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Current as of June 14, 2021 12:13 pm CDT  
800-533-1710 or 507-266-5700 or mayocliniclabs.com
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**54 Years** | **55 Years** | **56 Years** |
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57 Years 58 Years 59 Years
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60 Years 61 Years 62 Years
Female Male Female Male Female Male

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Current as of June 14, 2021 12:13 pm CDT
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**Clinical References:**
may have the potential to change the progression of the disease when given early. However, over 30% of patients fail to respond to anti-TNF-alpha therapy, and approximately 60% of patients who responded initially lose the response over time and require either drug dose-escalation or switch to an alternative agent in order to maintain response. Antidrug antibody formation may increase drug clearance in treated patients and/or neutralize the drug effect, thereby potentially contributing to the loss of response. Antidrug antibodies could also cause adverse events such as serum sickness and hypersensitivity reactions. Currently, adalimumab quantitation is commonly performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered in patients on therapy who are experiencing loss of response. Results from drug concentration measurement combined to ATA testing play an important role in patient management. When measured at trough, for patients who have undetectable or low concentrations of drug but no detectable ATA, the physician may choose to increase the dose of adalimumab in an attempt to increase the amount of the drug in circulation. If the patient has low adalimumab in the presence of an ATA, in many cases, the physician may switch the patient to another TNF inhibitor. In contrast, for patients with increased trough concentrations of adalimumab, whether or not an ATA is present, it may be necessary to switch the patient to a therapy with a different mechanism of action. For patients on biologics, assessing response to therapy is critical, since therapies are expensive and adverse events include greater risk for infections, such as reactivation of latent TB or hepatitis B, infusion or injection site reactions, cutaneous reactions, and reports of hepatotoxicity, demyelinating disease, and higher incidence of mortality and hospitalization in heart failure patients have been documented. Despite their therapeutic efficacy, more than one-third of patients on TNF inhibitors show no response to induction therapy (primary nonresponders) and in up to 50% of the responders, therapy becomes ineffective over time (secondary nonresponders). Reasons for primary loss of response are not well understood, but may include disease processes mediated by proinflammatory molecules other than TNF. Secondary loss of response, on the other hand, is associated with low albumin, high body-mass index, the degree of systemic inflammation and immune response to therapy, or immunogenicity. Laboratory testing of patients for quantitation of adalimumab and assessment of immunogenicity (development of autoantibodies against adalimumab) can help optimize therapy when partial response or loss of response to therapy are observed.

**Useful For:** Detection and quantification of antibodies directed against adalimumab in serum Trough level quantitation for evaluation of patients with loss of response to adalimumab

**Interpretation:** Currently, adalimumab quantitation is one of the most commonly tested monoclonal antibodies in routine practice; this testing is generally performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered for patients with inflammatory bowel disease (IBD) who are on adalimumab therapy and who are experiencing loss of response, but the testing may be ordered for anyone on adalimumab. Results from adalimumab and ATA testing play an important role in patient management. When measured at trough, for patients who have undetectable or low concentrations of adalimumab, but no detectable ATA, the physician may choose to increase the dose of adalimumab in an attempt to increase the amount of the drug in circulation. If the patient has low adalimumab in the presence of an ATA, in many cases the physician may switch the patient to another tumor necrosis factor (TNF) inhibitor. In contrast, for patients with increased trough concentrations of adalimumab, whether or not an ATA is present, it may be necessary to switch the patient to a therapy with a different mechanism of action, such as the anti-alpha4-beta-7-integrin antibody vedolizumab or the IL12/IL23 antibody ustekinumab, in the setting of IBD. Adalimumab quantitation will be interpreted in 2 different ways. When measured at trough, individuals may be considered to have adequate trough levels when drug concentrations are above 8 mcg/mL, and faster clearance of the drug, which may warrant a dosing adjustment or additional action if adalimumab trough concentration is below or equal to 8 mcg/mL. Adalimumab quantitation may influence patient management decisions as to whether therapy should continue as is, dose escalation is necessary, or a switch to a new therapeutic regimen is needed. Low trough concentrations may be correlated with loss of response to adalimumab. For adalimumab trough concentrations of 8.0 mcg/mL or less, testing for ATA is suggested. For adalimumab trough concentrations above 8.0 mcg/mL, the presence of ATA is unlikely; patients experiencing loss of response to adalimumab may benefit from an increased dose or more frequent dosing. Adalimumab concentration results above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough.

**Reference Values:**

**ADALIMUMAB QUANTITATIVE WITH REFLEX TO ANTIBODY**
Limit of quantitation is 0.8 mcg/mL. Optimal therapeutic ranges are disease specific.

**ADALIMUMAB ANTIBODY**

<14.0 AU/mL

**Clinical References:**

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**ADM13**

**ADAMTS13 Activity and Inhibitor Profile, Plasma**

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

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

**Interpretation:** Less than 10% ADAMTS13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting. The presence of ADAMTS13 inhibition (positive inhibitor screen) with a measurable antibody titer is most consistent with an acquired TTP.

**Reference Values:**

**ADAMTS13 ACTIVITY ASSAY**

> or =70%

**ADAMTS13 INHIBITOR SCREEN**
Negative

**ADAMTS13 BETHESDA TITER**
<0.4 BU

**Clinical References:**
3. Upshaw JD: Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and...
ADAMTS13 Inhibitor Bethesda Titer

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

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**Reference Values:**
Only orderable as part of a profile. For more information see ADM13 / ADAMTS13 Activity and Inhibitor Profile, Plasma.

- <0.4 BU

**Clinical References:**

ADAMTS13 Inhibitor Screen Assay

**Clinical Information:** Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy (TMA) syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and renal dysfunction. The large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy, and in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome), but far more commonly is acquired. Acquired TTP may be considered to be primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody
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**Reference Values:**
Only orderable as part of a profile. For more information see ADM13 / ADAMTS13 Activity and Inhibitor Profile, Plasma.

Negative


**ADSTM 62206** Additional Flow Stimulant (Bill Only)

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

**AGSTM 62208** Additional Flow Stimulant, LPAGF (Bill Only)

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

**MGSTM 62207** Additional Flow Stimulant, LPMGF (Bill Only)

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

**XSRM 607838** Additional Sample for Reflex Oligoclonal Banding, Serum

**Reference Values:**
Only orderable as part of a profile. For more information see:
-MSP3 / Multiple Sclerosis (MS) Profile, Serum and Spinal Fluid
-OLIG / Oligoclonal Banding, Serum and Spinal Fluid

Not Applicable
Additional Testing Virus Ident
Reference Values:
This test is for Billing Purposes Only.
This is not an orderable test.

Adenosine Deaminase in CSF
Reference Values:
0-9 U/L

Adenosine Deaminase in Peritoneal Fluid
Reference Values:
0 - 30 U/L

Adenosine Deaminase, Pericardial Fluid
Reference Values:
0-40 U/L

Adenosine Deaminase, Pleural Fluid
Reference Values:
0 - 30 U/L

Adenosine Deaminase, RBC
Interpretation: Adenosine Deaminase (ADA) deficiency is an autosomal recessive disorder of purine metabolism primarily affecting lymphocyte development, viability, and function. Affected individuals have less than 1 percent of normal ADA catalytic activity in red cell hemolysates. ADA deficiency is the cause of 20-30 percent of SCID cases. If the patient has been recently transfused, ADA deficiency may be masked; interpret results with caution. Heterozygotes cannot be identified by this test.
Reference Values:
400 - 900 mU/g Hb

Adenovirus DNA, Quantitative Real-Time PCR
Reference Values:
REFERENCE RANGE: <500 copies/mL

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

**Useful For:** Identification of adenovirus infection

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Adenovirus, Molecular Detection, PCR, Plasma**

**Clinical Information:** Human adenoviruses cause a variety of diseases including pneumonia, cystitis, conjunctivitis, diarrhea, hepatitis, myocarditis, and encephalitis. In humans, adenoviruses have been recovered from almost every organ system. Infections can occur at any time of the year and in all age groups. Currently, there are 57 adenovirus serotypes that have been grouped into 6 separate subgenera. Culture is the gold standard for the diagnosis for adenovirus infection; however, it can take up to 3 weeks to achieve culture results. Mayo's shell vial culture provides more rapid results, reported at 2 and 5 days. While PCR offers a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.

**Useful For:** Aiding in diagnosing adenovirus infections using plasma specimens

**Interpretation:** A positive result indicates the presence of adenovirus nucleic acid. A negative result does not rule out the presence of adenoviruses because organisms may be present at levels below the detection limits of this assay.

**Reference Values:**
Negative

**Clinical References:**
subgenera. Culture is the gold standard for the diagnosis for adenovirus infection. However, it can take up to 3 weeks to achieve culture results (Mayo Clinic's shell vial culture provides more rapid results, reported at 2 and 5 days). Serological tests have faster turnaround times, but can be less sensitive compared to culture. PCR offers a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.

**Useful For:** Aiding in the diagnosis of adenovirus infections

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

**Reference Values:**
Negative

**Clinical References:**

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**AKC**

**Adenylate Kinase Enzyme Activity, Blood**

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

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

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

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

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

Useful For: Evaluation of chronic nonspherocytic hemolytic anemia

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

Reference Values:
> or =12 months: 195-276 U/g Hb

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


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**FADIO 75607**

**Adiponectin Reference Values:**

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>Males (mcg/mL)</th>
<th>Females (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 25 kg/m²</td>
<td>4 - 26</td>
<td>5 - 37</td>
</tr>
<tr>
<td>25 - 30 kg/m²</td>
<td>4 - 20</td>
<td>5 - 28</td>
</tr>
<tr>
<td>Greater than 30 kg/m²</td>
<td>2 - 20</td>
<td>4 - 22</td>
</tr>
</tbody>
</table>

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**ACC 604986**

**Adrenal Mass Panel, 24 Hour, Urine Clinical Information:** Approximately 80 million computerized tomography (CT) scans are performed in the United States every year. Adrenal tumors are found incidentally in about 5% of these scans. Most of these tumors will turn out to be benign, but a small fraction will be adrenal cortical carcinoma (ACC), a type of cancer with high mortality and frequent recurrence. Even for localized disease, the 5 year survival rates do not exceed 65%, and distant spread is associated with a greater than 90% mortality rate within that time period. Early diagnosis of a malignant adrenal mass is therefore imperative to assure timely and appropriate therapy. Unfortunately, CT imaging alone is very limited in its ability to distinguish benign from malignant adrenal tumors since only very small and hypodense lesions can be easily dismissed as benign. The sizeable group of patients with larger or denser tumors ends up with an arduous workup that frequently includes additional imaging studies, hormonal testing, and biopsy. However, even the latter has both a high diagnostic false positive- and false negative rate, and ultimately the tumor is often resected, sometimes unnecessarily. On the other hand, the delays due to the diagnostic work might compromise optimal care for those tumors that prove malignant. In addition, patients who are believed to probably not have adrenal cancer after their workup, and those who opt out of biopsy or surgery, often still require long-term follow up with regular re-imaging and repeated hormone testing, with resultant radiation exposure and high health care costs. This adrenal mass panel is a noninvasive and more accurate test to diagnose malignant adrenal tumors, via urinary steroid profiling. It differentiates ACC, a rare and lethal tumor, from benign adrenocortical adenomas (ACA), including those that overproduce corticosteroids, or mineral steroids, or sex steroids, or those that are hormonally inactive. The test utilizes both clinical and laboratory data. The clinical parameters are age at diagnosis and sex of the patient, the size of the tumor by CT scanning and its x-ray density in Hounsfield units, whether it was detected incidentally or not, and whether there is evidence of hormone overproduction. All of this data are readily available for almost all patients with an adrenal mass, and are used by an algorithm to calculate the pretest probability of having ACC. The steroid profile testing is then performed and its results are added into the risk calculation algorithm to generate a posttest probability. The final result will provide the referring physicians a highly accurate probability for ACC and will thereby facilitate the optimal choice of further investigation, if any, based on an informed discussion between doctor and patient. Understanding the Adrenal Glands The human body has two adrenal glands, one above each kidney. Adrenal glands influence many processes and functions of our body, mainly through production of three types of steroid hormones: -Mineralocorticoids (eg, aldosterone, which helps control blood pressure) -Glucocorticoids (eg, cortisol, which is important for metabolism, immune response and stress) -Sex Steroids (eg, DHEAS, a precursor of testosterone and estradiol) These steroids are all synthesized from cholesterol via enzymes in the adrenal glands. In benign ACA, near-normal levels of precursor and bioactive steroids are produced. By contrast, ACC frequently shows abnormal patterns of steroid production. By measuring 25 different steroid metabolites, even subtle abnormalities can be detected. This is the basis for the assessment capability of profiling 25 steroids. Epidemiology of Adrenal Tumors Adrenal masses are found in 5% of
the population. The prevalence increases with age, to around 10% in 70-year-old patients. Although the majority of these tumors are benign, around 30% of adrenal tumors (>4cm) are malignant (most represented by ACCs), and the survival rate for these patients is very poor unless detected early.

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

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

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

Females 18-49 years:
Androsterone: 90-29,625 mcg/24 hour
Etiocholanolone: 127-24,568 mcg/24 hour
Dehydroepiandrosterone: <5-12,317 mcg/24 hour
16a-OH-Dehydroepiandrosterone: 5-31,248 mcg/24 hour
5-Pregnenetriol: 17-4,166 mcg/24 hour
5-Pregnenediol: 6-2,900 mcg/24 hour
Tetrahydro-11-Corticosterone: 13-1,548 mcg/24 hour
Tetrahydro-11-Deoxycorticosterone: <5-833 mcg/24 hour
17a-OH-Pregnanolone: 7-3,208 mcg/24 hour
Pregnanetriolone: <5-139 mcg/24 hour
Tetrahydrodeoxycortisol: 7-1,047 mcg/24 hour
Cortisol: 11-642 mcg/24 hour
6B-OH-Cortisol: 22-2,061 mcg/24 hour
Tetrahydrocortisol: 185-16,515 mcg/24 hour
5a-Tetrahydrocortisol: 45-22,591 mcg/24 hour
B-Cortol: 28-4260 mcg/24 hour
11B-OH-Androsterone: 59-12,462 mcg/24 hour
11B-OH-Etiocholanolone: 32-6,354 mcg/24 hour
Cortisone: 19-749 mcg/24 hour
Tetrahydrocortisone: 262-32,461 mcg/24 hour
a-Cortolone: 207-13,931 mcg/24 hour
B-Cortolone: 63-7,489 mcg/24 hour
11-Oxoetiocholanolone: 63-7,449 mcg/24 hour

Females > or =50 years:
Androsterone: 32-10,134 mcg/24 hour
Etiocholanolone: 52-10,946 mcg/24 hour
Dehydroepiandrosterone: <5-10,046 mcg/24 hour
<table>
<thead>
<tr>
<th>Compound</th>
<th>Level</th>
<th>Units</th>
<th>Males 18-49 years</th>
<th>Males &gt; or =50 years</th>
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<tbody>
<tr>
<td>16α-OH-Dehydroepiandrosterone</td>
<td>10-1,901 mcg/24 hour</td>
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<td>182-29,212 mcg/24 hour</td>
<td>118-25,389 mcg/24 hour</td>
</tr>
<tr>
<td>5-Pregnenetriol</td>
<td>5-2,732 mcg/24 hour</td>
<td></td>
<td>133-23,272 mcg/24 hour</td>
<td>127-15,640 mcg/24 hour</td>
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<tr>
<td>Tetrahydro-11-Corticosterone</td>
<td>14-1,229 mcg/24 hour</td>
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<td>Tetrahydro-11-Deoxycorticosterone</td>
<td>20-123 mcg/24 hour</td>
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<tr>
<td>Pregnanediol</td>
<td>8-2,138 mcg/24 hour</td>
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<tr>
<td>17α-OH-Pregnanolone</td>
<td>5-571 mcg/24 hour</td>
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<td>26-3,444 mcg/24 hour</td>
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<td>Cortisol</td>
<td>9-336 mcg/24 hour</td>
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<tr>
<td>6β-OH-Cortisol</td>
<td>25-1,365 mcg/24 hour</td>
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<td>B-Cortol</td>
<td>29-3289 mcg/24 hour</td>
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<td>11β-OH-Androsterone</td>
<td>86-9,280 mcg/24 hour</td>
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<td>11β-OH-Etiocholanolone</td>
<td>40-7,002 mcg/24 hour</td>
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<td>Cortisone</td>
<td>15-555 mcg/24 hour</td>
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<td>Tetrahydrocortisone</td>
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<td>α-Cortolone</td>
<td>125-17,472 mcg/24 hour</td>
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<td>B-Cortolone</td>
<td>82-5,784 mcg/24 hour</td>
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<tr>
<td>11-Oxoetiocholanolone</td>
<td>78-6,571 mcg/24 hour</td>
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<tr>
<td>Males 18-49 years:</td>
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</tr>
<tr>
<td>Androsterone</td>
<td>182-29,212 mcg/24 hour</td>
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<tr>
<td>Etiococholanolone</td>
<td>133-23,272 mcg/24 hour</td>
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<tr>
<td>Dehydroepiandrosterone</td>
<td>5-81,554 mcg/24 hour</td>
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<td>16α-OH-Dehydroepiandrosterone</td>
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<td>23-7,328 mcg/24 hour</td>
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<td>5-Pregnenediol</td>
<td>13-2,823 mcg/24 hour</td>
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<tr>
<td>Tetrahydro-11-Corticosterone</td>
<td>8-1,961 mcg/24 hour</td>
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<td>Tetrahydro-11-Deoxycorticosterone</td>
<td>&lt;5-316 mcg/24 hour</td>
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<td>Pregnanediol</td>
<td>12-3,812 mcg/24 hour</td>
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<td>17α-OH-Pregnanolone</td>
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<td>Pregnantriol</td>
<td>66-9,409 mcg/24 hour</td>
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<td>5-550 mcg/24 hour</td>
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<td>Tetrahydrodeoxycortisol</td>
<td>7-1520 mcg/24 hour</td>
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<td>Cortisol</td>
<td>5-903 mcg/24 hour</td>
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<tr>
<td>6β-OH-Cortisol</td>
<td>13-2,303 mcg/24 hour</td>
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<tr>
<td>Tetrahydrocortisol</td>
<td>152-22,723 mcg/24 hour</td>
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<tr>
<td>5α-Tetrahydrocortisol</td>
<td>157-24,059 mcg/24 hour</td>
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<td>B-Cortol</td>
<td>30-5,115 mcg/24 hour</td>
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<td>11β-OH-Etiocholanolone</td>
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<td>Cortisone</td>
<td>12-842 mcg/24 hour</td>
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<td>Tetrahydrocortisone</td>
<td>271-44,355 mcg/24 hour</td>
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<td>α-Cortolone</td>
<td>140-14,885 mcg/24 hour</td>
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<td>B-Cortolone</td>
<td>72-9,740 mcg/24 hour</td>
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<td>11-Oxoetiocholanolone</td>
<td>70-8,446 mcg/24 hour</td>
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<tr>
<td>Males &gt; or =50 years:</td>
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<tr>
<td>Androsterone</td>
<td>118-25,389 mcg/24 hour</td>
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<tr>
<td>Etiococholanolone</td>
<td>127-15,640 mcg/24 hour</td>
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<tr>
<td>Dehydroepiandrosterone</td>
<td>7-4,260 mcg/24 hour</td>
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<tr>
<td>16α-OH-Dehydroepiandrosterone</td>
<td>11-6,183 mcg/24 hour</td>
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<tr>
<td>5-Pregnenetriol</td>
<td>24-2,162 mcg/24 hour</td>
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<td>5-Pregnenediol</td>
<td>17-1,296 mcg/24 hour</td>
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<tr>
<td>Tetrahydro-11-Corticosterone</td>
<td>16-1,674 mcg/24 hour</td>
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</table>
Tetrahydro-11-Deoxycorticosterone: <5-297 mcg/24 hour
Pregnanediol: 23-1,846 mcg/24 hour
17a-OH-Pregnanolone: 18-1,747 mcg/24 hour
Pregnanetriol: 115-5,432 mcg/24 hour
Pregnanetriolone: 5-221 mcg/24 hour
Tetrahydrodeoxycortisol: 12-1,277 mcg/24 hour
Cortisol: 12-597 mcg/24 hour
6B-OH-Cortisol: 22-2,406 mcg/24 hour
Tetrahydrocortisol: 331-19,009 mcg/24 hour
5a-Tetrahydrocortisol: 155-3,266 mcg/24 hour
B-Cortol: 56-3,541 mcg/24 hour
11B-OH-Androsterone: 142-13,135 mcg/24 hour
11B-OH-Etiocholanolone: 69-6,805 mcg/24 hour
Cortisone: 24-732 mcg/24 hour
Tetrahydrocortisone: 454-34,576 mcg/24 hour
a-Cortolone: 211-17,591 mcg/24 hour
B-Cortolone: 114-8,434 mcg/24 hour
11-Oxoetiocholanolone: 155-7,174 mcg/24 hour

Clinical References:

Adrenocorticotrophic Hormone, ACTH, IgE, Serum

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

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

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

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


ACTH
70351

Adrenocorticotropin Hormone (ACTH) Immunostain, Technical Component Only

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

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

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


ACTH
8411

Adrenocorticotropin Hormone, Plasma

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

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

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


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

**ADULT 29345**

**Adulterants Survey, Random, Urine**

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

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

**Interpretation:** See Adulterant Survey Algorithm in Special Instructions.

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

**ISAE 45246**

**Aerobe Identification by Sequencing (Bill Only)**

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

**AERMC 604916**

**Aeromonas Culture, Feces**

**Clinical Information:** Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Aeromonas species are associated with a range of diarrheal presentations including acute secretory diarrhea with vomiting, chronic diarrhea lasting more than 10 days, and traveler’s diarrhea. Most cases of Aeromonas-associated diarrhea are self-limited and may be managed with supportive therapy (e.g., rehydration), but in severe cases or those in patients with a history of immunosuppression, antimicrobial therapy may be considered. Clinical studies have demonstrated differences in antimicrobial susceptibility profiles between Aeromonas species, highlighting the importance of both species identification and susceptibility testing for all isolates, particularly in serious infections.

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

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

**Reference Values:**
- No growth of pathogen

**Clinical References:**
AGXT Gene, Full Gene Analysis, Varies

Clinical Information: Primary hyperoxaluria type 1 (PH1) is a hereditary disorder of glyoxylate metabolism caused by deficiency of alanine:glyoxylate-aminotransferase (AGT), a hepatic enzyme that converts glyoxylate to glycine. Absence of AGT activity results in conversion of glyoxylate to oxalate, which is not capable of being degraded. Therefore, excess oxalate is excreted in the urine, causing kidney stones (urolithiasis), nephrocalcinosis, and kidney failure. As kidney function declines, blood levels of oxalate increase markedly, and oxalate combines with calcium to form calcium oxalate deposits in the kidney, eyes, heart, bones, and other organs, resulting in systemic disease. Pyridoxine (vitamin B6), a cofactor of AGT, is effective in reducing urine oxalate excretion in some PH1 patients. Presenting symptoms of PH1 include nephrolithiasis, nephrocalcinosis, or end-stage kidney disease with or without a history of urolithiasis. Age of symptom onset is variable; however, most individuals present in childhood or adolescence with symptoms related to kidney stones. In some infants with a more severe phenotype, kidney failure may be the initial presenting feature. Less frequently, affected individuals present in adulthood with recurrent kidney stones or kidney failure. End-stage kidney disease is most often seen in the third decade of life, but can occur at any age. The exact prevalence and incidence of PH1 are not known, but prevalence rates of 1 to 3 per million population and incidences of 0.1 per million/year have been estimated from population surveys. Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, 24 Hour, Urine). Abnormal urinary excretion of oxalate is strongly suggestive of, but not diagnostic for, this disorder, as there are other forms of inherited (type 2 and non-PH1/PH2) hyperoxaluria and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycolate in the presence of hyperoxaluria is suggestive of PH1. Historically, the diagnosis of PH1 was confirmed by AGT enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases. PH1 is inherited as an autosomal recessive disorder caused by mutations in the AGXT gene, which encodes the enzyme AGT. Several common AGXT mutations have been identified including c.33dupC, p.Gly170Arg (c.508G->A), and p.Ile244Thr (c.731T->C). These mutations account for at least 1 of the 2 affected alleles in approximately 70% of individuals with PH1. Direct sequencing of the AGXT gene is predicted to identify 99% of alleles in individuals who are known by enzyme analysis to be affected with PH1. While age of onset and severity of disease is variable and not necessarily predictable by genotype, a correlation between pyridoxine responsiveness and homozygosity for the p.Gly170Arg mutation has been observed. (Note: testing for the p.Gly170Arg mutation only is available by ordering AGXTG / Alanine:Glyoxylate Aminotransferase [AGXT] Mutation Analysis [G170R], Blood). Pyridoxine (vitamin B6) is a known cofactor of AGT and is effective in reducing urine oxalate excretion in some PH1 patients treated with pharmacologic doses. Individuals with 2 copies of the p.Gly170Arg mutation have been shown to normalize their urine oxalate when treated with pharmacologic doses of pyridoxine and those with a single copy of the mutation show reduction in urine oxalate. This is valuable because not all patients have been shown to be responsive to pyridoxine, and strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable.

Useful For: Confirming a diagnosis of primary hyperoxaluria type 1 Carrier testing for individuals with a family history of primary hyperoxaluria type 1 in the absence of known mutations in the family

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.


### ALT (8362)

**Alanine Aminotransferase (ALT) (GPT), Serum**

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

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

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

**Reference Values:**

Males

> or = 1 year: 7-55 U/L  
Reference values have not been established for patients who are <12 months of age.

Females

> or = 1 year: 7-45 U/L  
Reference values have not been established for patients who are <12 months of age.


### ALB24 (606718)

**Albumin, 24 Hour, Urine**

**Clinical Information:** Albumin excretion increases in patients with diabetes who are destined to develop diabetic nephropathy. More importantly, at this phase of increased albumin excretion before overt proteinuria develops, therapeutic maneuvers can be expected to significantly delay, or possibly prevent, development of nephropathy. These maneuvers include aggressive blood pressure maintenance

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

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

**Interpretation:** An albumin excretion rate of more than 30 mg/24 hours is considered to be microalbuminuric. By definition, the upper end of microalbuminuria is thought to be 300 mg/24 hours. Although this level has not been rigorously defined, it is felt that at this level it is more difficult to change the course of diabetic nephropathy. Laboratory normal values agree with the 30 mg/24 hour level. A normal excretion rate of 20 mcg/minute has also been established in the literature and is consistent with the laboratory data. Thus, microalbuminuria has been defined at 30 to 300 mg/24 hours. The literature has defined the albumin/creatinine ratio (mg/g) below 17 as normal for males and below 25 for females and is consistent with the laboratory's normal data. A ratio of albumin to creatinine of 300 or more indicates overt albuminuria. Thus, microalbuminuria has been defined as an albumin/creatinine ratio of 17 to 299 for males and 25 to 299 for females. Due to biologic variability, any patient who has an albumin/creatinine ratio or urinary albumin excretion rate in the positive microalbuminuria range should have this confirmed with a second specimen. If there is discrepancy, a third specimen is recommended. If 2 of 3 results are in the positive microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, aggressive blood pressure control, and institution of therapy with an angiotensin-converting enzyme inhibitor (if the patient can tolerate it).

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

**Clinical References:**
peritoneal cavity caused by changes in vascular permeability, hydrostatic pressure, and oncotic pressure. The most common causes of ascites in individuals are cirrhosis (80%), malignancy (10%), cardiac failure (5%), and infection. Total protein results of 3.0 g/dL or greater, historically used to classify ascites fluid as transudate or exudate, has a reported accuracy of only 55% in identifying exudates and has been largely replaced with measurement of the serum-ascites albumin gradient (SAAG), calculated as serum albumin concentration minus ascites albumin concentration. SAAG has been shown to correlate directly with portal pressure and SAAG results of 1.1 g/dL or greater are 97% accurate at identifying portal hypertension. Conditions associated with high SAAG include cirrhosis, acute liver failure, fatty liver disease, alcoholic hepatitis, portal vein thrombosis, hepatic malignancy, and veno-occlusive disease. Cardiac ascitic fluid caused by congestive heart failure has both a high SAAG result (> or =1.1 g/dL) and total protein concentration greater than 2.5 g/dL. Conditions associated with low SAAG measurement (<1.1 g/dL) include peritoneal malignancy, tuberculosis, pancreatitis, connective tissue disease, and nephrotic syndrome. Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end-stage renal disease, and heart failure that can lead to excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Dr. Richard Light derived criteria in the 1970s for patients with pleural effusions that are still used today.(2) Dr. Light's criteria were designed to be sensitive for detecting exudates at the expense of specificity.(3) Heart failure and recent diuretic use contribute to most misclassifications by Dr. Light's criteria (transudates falsely categorized as exudates). Serum-to-fluid protein or albumin gradient (serum protein or albumin minus fluid protein or albumin) may be calculated in these cases and when more than 3.1 g/dL (protein) or 1.2 g/dL (albumin) suggests the patient has a transudative effusion.

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

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

**Reference Values:**
An interpretive report will be provided

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

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

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

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

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

Clinical References:
albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control. The preferred specimen is a 24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin:creatinine ratio from a random urine specimen is also considered a valid screening tool. Several studies have addressed whether the specimen needs to be a fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

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

**Clinical References:**

**RALB1**  
**Albumin, Random, Urine**

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

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

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

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

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

**Clinical References:**

**ALB 8436**

**Albumin, Serum**

**Clinical Information:** Albumin is a carbohydrate-free protein, which constitutes 55% to 65% of total plasma protein. It maintains oncotic plasma pressure, is involved in the transport and storage of a wide variety of ligands, and is the source of endogenous amino acids. Albumin binds and solubilizes various compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Hypoalbuminemia is caused by several factors: impaired synthesis due either to liver disease (primary) or due to diminished protein intake (secondary), increased catabolism as a result of tissue damage and inflammation, malabsorption of amino acids, and increased renal excretion (eg, nephrotic syndrome).
### Albumin, Serum

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

**Useful For:** Assessing nutritional status

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

**Reference Values:**

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

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

**Clinical References:**
1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

### Albumin, Spinal Fluid

**Clinical Information:** Elevated albumin concentration in spinal fluid may serve as an indicator of the permeability status of the blood-brain barrier. Comparison to an ALB / Albumin, Serum concentration is recommended.

**Useful For:** Assessment of blood-brain barrier permeability

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

**Reference Values:**

- > or =12 months: 3500-5000 mg/dL

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

**Clinical References:**
1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018
**Albumin/Creatinine Ratio**

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

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

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

**Reference Values:**

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

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

Albuterol, Serum/Plasma

Reference Values:
Reporting limit determined each analysis

Synonym(s): Proventil

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

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

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

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

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

Aldolase, Serum

Clinical Information: Aldolase is necessary for glycolysis in muscle as a "rapid response" pathway for production of adenosine triphosphate, independent of tissue oxygen. Aldolase catalyzes the conversion of fructose 1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, an important reaction in the glycolytic breakdown of glucose to lactate in muscle. Aldolase is a tetramer whose primary structure depends upon the tissue from which it was synthesized (highest expression in liver, muscle, brain). Elevated values are found in muscle diseases, such as Duchenne muscular dystrophy, dermatomyositis, polymyositis, and limb-girdle dystrophy. While elevated creatinine kinase (CK) levels are more sensitive and specific for muscle disease, occasionally elevated aldolase is observed in some patients with myositis that have normal CK values.

Useful For: Detection of muscle disease

Interpretation: Measuring serum muscle enzymes is common in the evaluation of patients with muscle weakness or muscle myalgia. When elevated, serum muscle enzymes can help differentiate muscle disease derived muscle weakness from a neurogenic cause. The highest levels of aldolase are found in progressive (Duchenne) muscular dystrophy. Lesser elevations are found in dermatomyositis, polymyositis, and limb-girdle dystrophy. In dystrophic conditions causing hyperaldolasmia, the increase in aldolase becomes less dramatic as muscle mass decreases.
Reference Values:
<18 years: <14.5 U/L
> or =18 years: <7.7 U/L


ALDOSTERONE

Aldosterone with Sodium, 24 Hour, Urine

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

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

Interpretation: Under normal circumstances, if the 24-hour urinary sodium excretion is greater than 200 mEq, the urinary aldosterone excretion should be less than 10 mcg/24 hours. Urinary aldosterone excretion greater than 12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. Twenty-four hour urinary sodium excretion should exceed 200 mEq to document adequate sodium repletion. See Renin-Aldosterone Studies in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology; call 800-533-1710.

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


SODIUM
41-227 mmol/24 hours
If the 24-hour urinary sodium excretion is >200 mmol, the urinary aldosterone excretion should be <10 mcg.
**ALDU** 8556

**Aldosterone, 24 Hour, Urine**

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

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

**Interpretation:** Urinary aldosterone excretion greater than 12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. See Renin-Aldosterone Studies in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 days</td>
<td>0.7-11.0 mcg/24 hours*</td>
</tr>
<tr>
<td>31 days-11 months</td>
<td>0.7-22.0 mcg/24 hours*</td>
</tr>
<tr>
<td>&gt; or =1 year</td>
<td>2.0-20.0 mcg/24 hours</td>
</tr>
</tbody>
</table>


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


**APIVC** 65425

**Aldosterone, Inferior Vena Cava, Plasma**

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

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

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

**Reference Values:**
No established reference values.

**Clinical References:**

**AIVC 6503**

**Aldosterone, Inferior Vena Cava, Serum**

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

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

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

**Reference Values:**
No established reference values.

**Clinical References:**
2. Young WF Jr: Pheochromocytoma and primary
**Aldosterone, Left Adrenal Vein, Plasma**

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

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

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

**Reference Values:**
No established reference values.

**Clinical References:**

**Aldosterone, Left Adrenal Vein, Serum**

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

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

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

**Reference Values:**
No established reference values.

**Clinical References:**

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**Aldosterone, Plasma**

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

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

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

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


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

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

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

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

Reference Values: No established reference values.


Aldosterone, Right Adrenal Vein, Serum

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

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

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

Reference Values: No established reference values.

ALDS 8557

Aldosterone, Serum

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

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

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

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


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


FALPE 57945

Alfalfa (Medicago sativa) IgE

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

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 117
Alkaline Phosphatase, Serum

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

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

Interpretation: Increases in serum alkaline phosphatase (ALP) activity commonly originate from 1 or both of 2 sources: liver and bone. Consequently, serum ALP measurements are of particular interest in the investigation of 2 groups of conditions: hepatobiliary disease and bone disease associated with increased osteoblastic activity. Serum ALP was the first enzyme to be used for the investigation of hepatic disease. The response of the liver to any form of biliary tree obstruction induces the synthesis of ALP by hepatocytes. The newly formed coenzyme is released from the cell membrane by the action of bile salts and enters the circulation to increase the enzyme activity in serum. Increase tends to be more notable (greater than 4-fold the upper reference value [URV]) in extrahepatic obstruction (eg, by stone, by cancer of the head of the pancreas) than in intrahepatic obstruction, and is greater the more complete the obstruction. Serum enzyme activities may reach 10 to 12 times the URV and usually return to baseline on surgical removal of the obstruction. A similar increase is seen in patients with advanced primary liver cancer or widespread secondary hepatic metastases. ALP increase (greater than 2-fold the URV) can predict transplant-free survival rates of patients with primary biliary cirrhosis. Liver diseases that principally affect parenchymal cells, such as infectious hepatitis, typically show only moderately (less than 3-fold) increased or even normal serum ALP activities. Increases may also be seen as a consequence of a reaction to drug therapy, and ALT/ALP-based criteria to discriminate the type of liver injury in drug-induced hepatic toxicity have been recommended. Intestinal ALP isoenzyme, an asialoglycoprotein normally cleared by the hepatic asialoglycoprotein receptors, is often increased in patients with liver cirrhosis.

Reference Values:

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

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

Reference Values:

<0.35 kU/L

Alkaline Phosphatase, Total and Isoenzymes, Serum

Clinical Information: Alkaline phosphatase (ALP) is present in a number of tissues including liver, bone, intestine, and placenta. The activity of ALP found in serum is a composite of isoenzymes from those sites and, in some circumstances, placental or Regan isoenzymes. Serum ALP is of interest in the diagnosis of 2 main groups of conditions-hepatobiliary disease and bone disease associated with increased osteoblastic activity. A rise in ALP activity occurs with all forms of cholestasis, particularly with obstructive jaundice. The response of the liver to any form of biliary tree obstruction is to synthesize more ALP. The main site of new enzyme synthesis is the hepatocytes adjacent to the biliary canaliculi. ALP is also elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling, such as Paget disease, rickets, osteomalacia, fractures, and malignant tumors. Moderate elevation of ALP may be seen in other disorders such as Hodgkin disease, congestive heart failure, ulcerative colitis, regional enteritis, and intra-abdominal bacterial infections.

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

Interpretation: Total Alkaline Phosphatase: Alkaline phosphatase (ALP) elevations tend to be more marked (more than 3-fold) in extrahepatic biliary obstructions (eg, by stone or cancer of the head of the pancreas) than in intrahepatic obstructions; the more complete the obstruction, the greater the elevation. With obstruction, serum ALP activities may reach 10 to 12 times the upper limit of normal, returning to normal upon surgical removal of the obstruction. The ALP response to cholestatic liver disease is similar to the response of gamma-glutamyltransferase (GGT) but more blunted. If both GGT and ALP are elevated, a liver source of the ALP is likely. Among bone diseases, the highest level of ALP activity is encountered in Paget disease, as a result of the action of the osteoblastic cells as they try to rebuild bone that is being resorbed by the uncontrolled activity of osteoclasts. Values from 10 to 25 times the upper limit of normal are not unusual. Only moderate rises are observed in osteomalacia, while levels are generally normal in osteoporosis. In rickets, levels 2 to 4 times normal may be observed. Primary and secondary hyperparathyroidism are associated with slight to moderate elevations of ALP; the existence and degree of elevation reflects the presence and extent of skeletal involvement. Very high enzyme levels are present in patients with osteogenic bone cancer. A considerable rise in ALP is seen in children following accelerated bone growth. ALP increases of 2 to 3 times normal may be observed in women in the third trimester of pregnancy, although the reference interval is very wide and levels may not exceed the upper limit of normal in some cases. In pregnancy, the additional enzyme is of placental origin. ALP Isoenzymes: Liver ALP isoenzyme is associated with biliary epithelium and is elevated in cholestatic processes. Various liver diseases (primary or secondary cancer, biliary obstruction) increase the liver isoenzyme. Liver 1 (L1) is increased in some nonmalignant diseases (such as cholestasis, cirrhosis, viral hepatitis, and in various biliary and hepatic pathologies). It is also increased in malignancies with hepatic metastasis, in cancer of the lungs and digestive tract, and in lymphoma. An increase of liver 2 (L2) may occur in cholestasis and biliary diseases (eg, cirrhosis, viral hepatitis) and in malignancies (eg, breast, liver, lung, prostate, digestive tract) with liver metastasis. Osteoblastic bone tumors and hyperactivity of osteoblasts involved in bone remodeling (eg, Paget disease) increase the bone isoenzyme. Paget disease leads to a striking, solitary elevation of bone ALP. The intestinal isoenzyme may be increased in patients with cirrhosis and in individuals who are blood group O or B secretors. The placental (carcino-placental antigen) and Regan isoenzyme can be elevated...
in cancer patients.

Reference Values:

ALKALINE PHOSPHATASE

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

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

ALKALINE PHOSPHATASE ISOENZYMES

Liver 1%
0-6 years: 5.1-49.0%
7-9 years: 3.0-45.0%
10-13 years: 2.9-46.3%
14-15 years: 7.8-48.9%
16-18 years: 14.9-50.5%
> or =19 years: 27.8-76.3%

Liver 1
0-6 years: 7.0-112.7 IU/L
7-9 years: 7.4-109.1 IU/L
10-13 years: 7.8-87.6 IU/L
14-15 years: 10.3-75.6 IU/L
16-18 years: 13.7-78.5 IU/L
> or =19 years: 16.2-70.2 IU/L

Liver 2%
0-6 years: 2.9-13.7%
7-9 years: 3.7-12.5%
10-13 years: 2.9-22.3%
14-15 years: 2.2-19.8%
16-18 years: 1.9-12.5%
> or =19 years: 0.0-8.0%

Liver 2
0-6 years: 3.0-41.5 IU/L
7-9 years: 4.0-35.6 IU/L
10-13 years: 3.3-37.8 IU/L
14-15 years: 2.2-32.1 IU/L
16-18 years: 1.4-19.7 IU/L
> or =19 years: 0.0-5.8 IU/L

Bone %
0-6 years: 41.5-82.7%
7-9 years: 39.9-85.8%
10-13 years: 31.8-91.1%
14-15 years: 30.6-85.4%
16-18 years: 38.9-72.6%
> or =19 years: 19.1-67.7%
Bone
0-6 years: 43.5-208.1 IU/L
7-9 years: 41.0-258.3 IU/L
10-13 years: 39.4-346.1 IU/L
14-15 years: 36.4-320.5 IU/L
16-18 years: 32.7-214.6 IU/L
> or =19 years: 12.1-42.7 IU/L

Intestine %
0-6 years: 0.0-18.4%
7-9 years: 0.0-18.3%
10-13 years: 0.0-11.8%
14-15 years: 0.0-8.2%
16-18 years: 0.0-8.7%
> or =19 years: 0.0-20.6%

Intestine
0-6 years: 0.0-37.7 IU/L
7-9 years: 0.0-45.6 IU/L
10-13 years: 0.0-40.0 IU/L
14-15 years: 0.0-26.4 IU/L
16-18 years: 0.0-12.7 IU/L
> or =19 years: 0.0-11.0 IU/L

Placental
Not present

Clinical References:
1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018
10 year 7-110
11-14 year 7-111
15-19 year 6-96
20-30 year 4-59
31-50 year 5-79
51-80 year 3-48

Aspergillus fumigatus IgE <0.35 kU/L
Aspergillus fumigatus IgG <46 mcg/mL
A. fumigatus Mix Gel Diffusion Negative

The gel diffusion method was used to test this patient’s serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms. This test was developed and its performance characteristics determined by Viracor Eurofins. It has not been cleared or approved by the FDA.

Patients with allergic bronchopulmonary aspergillosis (ABPA) are expected to have the following serological features:

1) A high total IgE of >500 IU/mL, unless patient is receiving corticosteroids.
2) An elevated Aspergillus-specific IgE of class 4 or higher.
3) Positive for Aspergillus-specific IgG.

Allo-isoleucine, Blood Spot

**Clinical Information:** Maple-syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain-ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). Classic MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple-syrup odor to urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. MSUD is a pan-ethnic condition but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1:760 live births. The incidence of MSUD is approximately 1:200,000 live births in the general population. Newborn screening includes the measurement of BCAA (Leu, Ile, and Val), which are elevated in MSUD. However, unaffected infants receiving total parenteral nutrition frequently have increased levels of BCAA, a situation that often triggers unnecessary follow-up investigations. Abnormal concentrations of allo-isoleucine (Allo-Ile) are pathognomonic for MSUD. The determination of Allo-Ile (second-tier testing) in the same newborn screening specimens that reveals elevated BCAA allows for positive identification of patients with MSUD and differentiation from BCAA elevations due to dietary artifacts, reducing the occurrence of false-positive newborn screening results. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. BCAA are essential amino acids, which require frequent adjustment of the dietary treatment. Dietary monitoring is accomplished by regular determination of BCAA and Allo-Ile concentrations.

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

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

**Reference Values:**
Allo-isoleucine: <2 nmol/mL
Leucine: 35-215 nmol/mL
Isoleucine: 13-130 nmol/mL
Valine: 51-325 nmol/mL
An interpretive report will also be provided.


Clinical Information: Autoimmune lymphoproliferative syndrome (ALPS) (also known as Canale-Smith syndrome) is a complex clinical disorder of dysregulated lymphocyte homeostasis that is characterized by lymphoproliferative disease, autoimmune cytopenias, splenomegaly, and lymphadenopathy with an increased susceptibility to malignancy.(1) Typically, ALPS is diagnosed by childhood or young adulthood. Genetic defects in the apoptosis (programmed cell death) pathway have been determined for most cases of ALPS. Apoptosis plays a role in normal immune homeostasis by limiting lymphocyte accumulation and autoimmune reactivity. The interaction of the surface receptor CD95 (FAS) and its ligand (CD95L;FASL) triggers the apoptotic pathway in lymphocytes. The following molecular ALPS classification has been established: ALPS Classification Molecular/Genetic Defect in Apoptosis Type Ia CD95 (FAS) mutations(1) Type Ib Heterozygous CD95L (FASLG) mutations(1) Type Ic Homozygous CD95L (FASLG) mutation(2) Type II CASP8 or CASP10 mutations(1,3) Type III Unknown(1,3) Patients with ALPS have an increase in a normally rare population of T cells (typically <1%) that are alpha beta T-cell receptor (TCR)-positive, as well as negative for both CD4 and CD8 coreceptors (double-negative T cells: DNT).(1) The alpha beta TCR+DNT cells from ALPS patients also express an unusual B-cell-specific CD45R isoform, called B220.(4,5) B220 expression on alpha beta TCR+DNT cells has been demonstrated to be a sensitive and specific marker for ALPS and is associated with FAS mutations.(4) Several other diseases can present with an ALPS-like phenotype, including independent conditions like Evans syndrome (a combination of autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura), Rosai-Dorfman disease (massive painless cervical lymphadenopathy that may be accompanied by leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia), and nodular lymphocyte-predominant Hodgkin disease.(1)

Useful For: Diagnosing autoimmune lymphoproliferative syndrome, primarily in patients <45 years of age

Interpretation: The presence of increased circulating T cells (CD3+) that are negative for CD4 and CD8 (double-negative T cells: DNT) and positive for the alpha/beta T-cell receptor (TCR) is required for the diagnosis of autoimmune lymphoproliferative syndrome (ALPS). The laboratory finding of increased alpha beta TCR+DNT cells is consistent with ALPS only with the appropriate clinical picture (nonmalignant lymphadenopathy, splenomegaly, and autoimmune cytopenias). Conversely, there are other immunological disorders, including common variable immunodeficiency (CVID), which have subsets for patients with this clinical picture, but no increase in alpha beta TCR+DNT cells. If the percent of the absolute count of either the alpha beta TCR+DNT cells or alpha beta TCR+DNT B220+ cells is abnormal, additional testing is indicated. All abnormal alpha beta TCR+DNT cell results should be confirmed (for ALPS) with additional testing for defective in vitro lymphocyte apoptosis, followed by confirmatory genetic testing for FAS mutations (call 800-533-1710 for test forwarding information).

Reference Values:
Alpha beta TCR+DNT cells
2-18 years: <2% CD3 T cells
19-70+ years: <3% CD3 T cells
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT cells
2-18 years: <35 cells/mcL
19-70+ years: <35 cells/mcL
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <0.4% CD3 T cells
19-70+ years: <0.3% CD3 T cells
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <7 cells/mcL
19-70+ years: <6 cells/mcL
Reference values have not been established for patients that are less than 24 months of age.


**Alpha Defensin, Lateral Flow Assay, Synovial Fluid**

**Clinical Information:** Diagnosis of prosthetic joint infections (PJI) may be challenging in certain clinical scenarios. Multiple societies have defined criteria for establishing the presence of a PJI, including results from laboratory tests, clinical findings, and tissue histopathology. The challenge, however, is that results of these tests are frequently not available at the time of or after surgery. As an alternative, determining the cell count and differential on synovial fluid are frequently used biomarkers for PJI, however there is a lack of consensus on the optimal thresholds to use for a PJI diagnosis. Additionally, cell count and differential results require clinician interpretation as laboratories do not report abnormal levels correlating with PJI. Alpha defensins are antimicrobial peptides released by activated neutrophils in response to infection and served as part of the host-defense innate immune system with broad antimicrobial activity against Gram-positive and Gram-negative bacteria, mycobacteria, fungi, and viruses. The presence of alpha defensins in synovial fluid may therefore be used by clinicians as a marker of PJI.

**Useful For:** Detection of alpha defensins 1-3, human host response proteins, in synovial fluid of adults with a total joint replacement who are being evaluated for revision surgery This test is not intended to be used to determine timing for reimplantation in 2-stage procedures.

**Interpretation:** Negative: No alpha defensin detected in synovial fluid, suggesting absence of prosthetic joint infection. Positive: Alpha defensin in synovial fluid detected suggesting presence of prosthetic joint infection. Additional microbiologic studies (eg, culture, molecular detection) are recommended.

**Reference Values:**
Negative
Reference values apply to all ages.
Alpha Follicle Stimulating Hormone Immunostain, Technical Component Only

**Clinical Information:** Follicle stimulating hormone (FSH) alpha subunit is a component common to all glycoprotein hormones produced by the anterior pituitary (luteinizing hormone [LH], thyroid-stimulating hormone [TSH], and FSH). Glycoprotein hormone-producing cells (approximately 30% of the total cell population) in normal pituitary stain in a cytoplasmic pattern. Immunohistochemical detection of alpha-FSH may be useful in the classification of pituitary adenomas.

**Useful For:** May aid in the classification of pituitary adenomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Alpha Globin Gene Sequencing, Blood

**Clinical Information:** Alpha-globin gene sequencing detects alpha-globin variants and nondeletional alpha thalassemia variants. Alpha thalassemia is the most common monogenic condition in the world. It is estimated that up to 5% of the world's population carries at least 1 alpha thalassemia variant and, in the United States, approximately 30% of African Americans are thought to carry an alpha thalassemia variant. Alpha thalassemia variants are most common in individuals of Southeastern Asian, African, Mediterranean, Indian, and Middle-Eastern descent, but they can be found in persons from any ethnic group. Four alpha-globin genes are normally present, 2 copies on each chromosome 16. Alpha thalassemia variants result in decreased alpha-globin chain production. In general, alpha thalassemia is characterized by hypochromic, microcytic anemia and varies clinically from asymptomatic (alpha thalassemia silent carrier and alpha thalassemia trait) to lethal hemolytic anemia (hemoglobin [Hb] Barts hydrops fetalis). Large deletions of the alpha-globin genes account for approximately 90% of alpha thalassemia alterations, and these will not be detected by alpha-globin gene sequencing. Other alterations, such as point alterations or small deletions within the alpha-globin genes, account for most of the remaining 10% of alpha thalassemia variants. These nondeletional subtypes can be detected by alpha-globin gene sequencing. The most common nondeletional alpha thalassemia variant is Hb Constant Spring (HbCS). The majority of alpha-globin chain variants are clinically and hematologically benign; however, some cause erythrocytosis and chronic hemolytic anemia. Hemoglobin electrophoresis may not be able to confirm their identity. In these instances, alpha-globin gene sequencing can be useful.

**Useful For:** Testing for nondeletional alpha thalassemia in a symptomatic individual Follow-up testing to an abnormal hemoglobin electrophoresis that identified an alpha-globin chain variant Evaluating for nondeletional alpha thalassemias in an algorithmic process for: -HAEV1 / Hemolytic Anemia Evaluation, Blood -HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood -MEV1 / Methemoglobinemia Evaluation, Blood -REVE1 / Erythrocytosis Evaluation, Whole Blood -THEV1 / Thalassemia and
Hemoglobinopathy Evaluation, Blood and Serum

**Interpretation:** An summary interpretation will be provided as a part of the HAEV1 / Hemolytic Anemia Evaluation, Blood; HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood; MEV1 / Methemoglobinemia Evaluation, Blood; REVE1 / Erythrocytosis Evaluation, Whole Blood; THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum.

**Reference Values:**
Only orderable as a reflex. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

**Clinical References:**

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**Alpha Globin Gene Sequencing, Varies**

**Clinical Information:** Alpha globin gene sequencing detects alpha globin variants and nondeleitional alpha thalassemia variants. Alpha thalassemia is the most common monogenic condition in the world. It is estimated that up to 5% of the world’s population carries at least 1 alpha thalassemia variant and, in the United States, approximately 30% of African Americans are thought to carry an alpha thalassemia variant. Alpha thalassemia variations are most common in individuals of Southeastern Asian, African, Mediterranean, Indian, and Middle Eastern descent, but they can be found in persons from any ethnic group. Four alpha-globin genes are normally present, 2 copies on each chromosome 16. Alpha thalassemia variants result in decreased alpha-globin chain production. In general, alpha thalassemia is characterized by hypochromic, microcytic anemia and varies clinically from asymptomatic (alpha thalassemia silent carrier and alpha thalassemia trait) to lethal hemolytic anemia (hemoglobin: Hb Barts hydrops fetalis). Large deletions of the alpha globin genes account for approximately 90% of alpha thalassemia alterations, and these variations will not be detected by alpha-globin gene sequencing. Other variants, such as point alterations or small deletions within the alpha-globin genes, account for most of the remaining 10% of alpha thalassemia variations. These nondeleitional subtypes can be detected by alpha globin gene sequencing. The most common nondeleitional alpha thalassemia variant is Hb Constant Spring (HbCS). The majority of alpha globin chain variants are clinically and hematologically benign however, some cause erythrocytosis and chronic hemolytic anemia. Hemoglobin electrophoresis may not be able to confirm their identity. In these instances, alpha-globin gene sequencing can be useful.

**Useful For:** Diagnosing nondeleitional alpha thalassemia Testing for nondeleitional alpha thalassemia in a symptomatic individual Follow-up testing to an abnormal hemoglobin electrophoresis that identified an alpha-globin chain variant

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FALG**

**Alpha Lactalbumin IgG**

**Interpretation:**

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

**ASYN**

**Alpha Synuclein Immunostain, Technical Component Only**

**Clinical Information:** Alpha synuclein is a member of a family of cytoplasmic proteins found predominantly in the presynaptic nerve terminal of the brain. Synucleins are thought to be involved in neuronal plasticity, synaptic function, and neurodegenerative disease. Alpha-synuclein is abundant in Lewy bodies in sporadic Parkinson disease and dementia with Lewy bodies. It is a major component of amyloid plaques in Alzheimer disease.

**Useful For:** Identification of alpha synuclein in neurogenerative disorders

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FA1GP**

**Alpha-1-Acid Glycoprotein**

**Reference Values:**
Adults:  39 – 115 mg/dL

**A1AFS**

**Alpha-1-Antitrypsin Clearance, Feces and Serum**

**Clinical Information:** Alpha-1-antitrypsin (AAT) is a 54kDa glycoprotein that is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of
blood proteins in the intestinal tract. AAT clearance is reliable for measuring protein loss distal to the pylorus. A serum sample is required to interpret results as a serum deficiency of AAT would make the AAT fecal excretion lower and could invalidate the test utility. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow's milk. Increased fecal excretion of AAT can be found in small and large intestine disease and is applicable to adult and children.

**Useful For:** Diagnosing protein-losing enteropathies

**Interpretation:** Elevated alpha-1-antitrypsin (AAT) clearance suggests excessive gastrointestinal protein loss. The positive predictive value of the test has been found to be 97.7% and the negative predictive value is 75%. Patients with protein-losing enteropathies generally have AAT clearance values greater than 50 mL/24 hours and AAT fecal concentrations above 100 mg/dL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

**Reference Values:**

- **CLEARANCE:**
  - \(< \text{ or } = 27 \text{ mL/24 hours}\)

- **FECAL ALPHA-1-ANTRYPSIN CONCENTRATION:**
  - \(< \text{ or } = 54 \text{ mg/dL}\)

- **SERUM ALPHA-1-ANTRYPSIN CONCENTRATION:**
  - 100-190 mg/dL

**Clinical References:**


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**AATRP**

**Alpha-1-Antitrypsin Immunostain, Technical Component Only**

**Clinical Information:** Alpha-1-antitrypsin (AAT) is a plasma protein synthesized in the liver and is present in serum and tissue fluids where it acts as an inhibitor of proteases, especially elastase. AAT deficiency is associated with development of emphysema and liver disease. In liver disease, abnormal accumulation of AAT is seen as cytoplasmic globules in hepatocytes.

**Useful For:** Identification of abnormal accumulation of alpha-1-antitrypsin

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality is recommended. This test is performed using antibodies directed against AAT. The AATRP 70350Alpha-1-Antitrypsin Immunostain, Technical Component Only requires a tissue sample for analysis.
control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


### A1APP

#### Alpha-1-Antitrypsin Phenotype, Serum

**Clinical Information:** Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. Most normal individuals have the M phenotype (M, M1, or M2). Over 99% of M phenotypes are genetically MM. In the absence of family studies, the phenotype (M) and quantitative level can be used to infer the genotype (MM). The most common alleles associated with a quantitative deficiency are Z and S. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

**Useful For:** Identification of homozygous and heterozygous phenotypes of the alpha-1-antitrypsin deficiency

**Interpretation:** There are greater than 40 alpha-1-antitrypsin (A1A) phenotypes (most of these are associated with normal quantitative levels of protein). The most common normal phenotype is M (M, M1, or M2), and greater than 90% of Caucasians are genetically homozygous M (MM). A1A deficiency is usually associated with the Z phenotype (homozygous ZZ), but SS and SZ are also associated with decreased A1A levels.

**Reference Values:**

- **ALPHA-1-ANTITRYPSIN**
  - 100-190 mg/dL

**Clinical References:**


### A1ALC

#### Alpha-1-Antitrypsin Proteotype S/Z by LC-MS/MS, Serum

**Clinical Information:** Alpha-1-antitrypsin (A1A) is a protein that inhibits the enzyme neutrophil elastase. It is predominantly synthesized in the liver and secreted into the bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema, which initially affects the lung bases (as opposed to smoking-related emphysema, which presents with upper-lung field emphysema). Patients may become symptomatic in their 30s and 40s. The most frequent symptoms reported in a National Institute of Health study of 1,129 patients with severe deficiency (mean age 46 years) included cough (42%), wheezing (65%), and dyspnea with exertion (84%). Many patients were misdiagnosed as having asthma. It is estimated that approximately one-sixth of all lung transplants are for A1A deficiency. Liver disease can also occur, particularly in children; it
occurs much less commonly than emphysema in adults. A1A deficiency is a relatively common disorder in Northern European Caucasians. The diagnosis of A1A deficiency is initially made by quantitation of protein levels in serum followed by determination of specific allelic variants by isoelectric focusing (IEF). While there are many different alleles in this gene, only 3 are common. The 3 major alleles include: M (full functioning, normal allele), S (associated with reduced levels of protein), and Z (disease-causing mutation associated with liver disease and premature emphysema). The S and Z alleles account for the majority of the abnormal alleles detected in affected patients. As a codominant disorder, both alleles are expressed. An individual of SZ or S-null genotype may have a small increased risk for emphysema (but not liver disease) due to slightly reduced protein levels. On the other hand, an individual with the ZZ genotype is at greater risk for early onset liver disease and premature emphysema. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. Historically, IEF has been the primary method for characterizing variants, though in some cases the interpretation is difficult and prone to error. Serum quantitation is helpful in establishing a diagnosis, but can be influenced by other factors. A proteomic method using trypsin-digested sera can detect the mutated peptides of the S and Z alleles, but can miss disease alleles other than the S and Z alleles. This test combines all of these methods to provide a comprehensive result.

Useful For: Determining the specific proteotype for prognosis and genetic counseling for patients with alpha-1-antitrypsin deficiency

Interpretation: For each of the possible alpha-1-antitrypsin (A1A) genotypes there is an expected range for the total serum level of A1A. However, a number of factors can influence either the A1A serum level or the A1A proteotype results, including acute illness (A1A is an acute-phase reactant), protein replacement therapy, the presence of other rare variants, or the presence of DNA polymorphisms. When the serum level differs from what is expected for that proteotype (ie, discordant), additional studies are performed to ensure the most appropriate interpretation of test results. Additional follow-up may include A1A phenotyping by isoelectric focusing, obtaining additional clinical information, and DNA sequencing. See Alpha-1-Antitrypsin Testing Result Table in Special Instructions.

Reference Values:
ALPHA-1-ANTITRYPSIN
100-190 mg/dL

ALPHA-1-ANTITRYPSIN PROTEOTYPE
Negative for S and Z phenotype (Non S Non Z)


A1AF

Alpha-1-Antitrypsin, Random, Feces

Clinical Information: Alpha-1-antitrypsin (AAT) is a 54kDa glycoprotein that is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. AAT clearance is reliable for measuring protein loss distal to the pylorus. A serum sample is required to interpret results as a serum deficiency of AAT would make the AAT fecal excretion lower and could invalidate the test utility. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow’s milk. Increased fecal excretion of AAT can be found in small and large intestine disease and is applicable to adults and children.

Useful For: Diagnosing protein-losing enteropathies, especially when used in conjunction with serum alpha-1-antitrypsin (AAT) levels as a part of AAT clearance studies
Interpretation: Patients with protein-losing enteropathies generally have alpha-1-antitrypsin fecal concentrations over 100 mg/dL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

Reference Values:
< or =54 mg/dL


**AAT**

**Alpha-1-Antitrypsin, Serum**

Clinical Information: Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

Useful For: Workup of individuals with suspected disorders such as familial chronic obstructive lung disease Diagnosis of alpha-1-antitrypsin deficiency

Interpretation: Patients with serum levels less than 70 mg/dL may have a homozygous deficiency and are at risk for early lung disease. Alpha-1-antitrypsin proteotyping should be done to confirm the presence of homozygous deficiency alleles. If clinically indicated, patients with serum levels less than 125 mg/dL should be proteotyped in order to identify heterozygous individuals. Heterozygotes do not appear to be at increased risk for early emphysema.

Reference Values:
100-190 mg/dL


**A1M24**

**Alpha-1-Microglobulin, 24 Hour, Urine**

Clinical Information: Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily. It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated excretion. Elevated alpha-1-microglobulin in
patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

**Useful For:** Assessment of renal tubular injury or dysfunction Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

**Interpretation:** Alpha-1-microglobulin above the reference values may be indicative of a proximal tubular dysfunction.

**Reference Values:**

- > or =16 years: <19 mg/24 hours
- 7 mg/g creatinine is a literature suggested upper reference limit for pediatrics 1 month to 15 years of age.*


**Clinical References:**


**Alpha-1-Microglobulin, Random, Urine**

**Clinical Information:** Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily. It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrototoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated urinary alpha-1-microglobulin excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

**Useful For:** Assessment of renal tubular injury or dysfunction Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

**Interpretation:** Alpha-1-microglobulin above the reference values may be indicative of a proximal tubular dysfunction. As suggested in the literature, 7 mg/g creatinine is an upper reference limit for pediatric patients of 1 month to 15 years of age.

**Reference Values:**
<50 years: <13 mg/g creatinine
> or =50 years: <20 mg/g creatinine

**Clinical References:**

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**A2PI**

**Alpha-2 Plasmin Inhibitor, Plasma**

**Clinical Information:** Alpha-2 plasmin inhibitor (antiplasmin) is synthesized in the liver with a biological half-life of approximately 3 days. It inactivates plasmin, the primary fibrinolytic enzyme responsible for remodeling the fibrin thrombus, and binds fibrin, together with factor XIIIa, making the clot more difficult to lyse. Absence of alpha-2 plasmin inhibitor results in uncontrolled plasmin-mediated breakdown of the fibrin clot and is associated with increased risk of bleeding.

**Useful For:** Diagnosing congenital alpha-2 plasmin inhibitor deficiencies (rare) Providing a more complete assessment of disseminated intravascular coagulation, intravascular coagulation and fibrinolysis, or hyperfibrinolysis (primary fibrinolysis), when measured in conjunction with fibrinogen, fibrin D-dimer, fibrin degradation products, soluble fibrin monomer complex, and plasminogen Evaluating liver disease Evaluating the effects of fibrinolytic or antifibrinolytic therapy

**Interpretation:** Patients with congenital homozygous deficiency (with levels of <10%) are clinically affected (bleeding). Heterozygotes having levels of 30% to 60% of mean normal activity are usually asymptomatic. Lower than normal levels may be suggestive of consumption due to activation of plasminogen and its inhibition by alpha-2 plasmin inhibitor. The clinical significance of high levels of alpha-2 plasmin inhibitor is unknown.

**Reference Values:**

Adults: 80-140%

Normal, full-term, and premature infants may have mildly decreased levels (> or =50%) which reach adult levels < or = 90 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Clinical References:**

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**A2M**

**Alpha-2-Macroglobulin, Serum**

**Clinical Information:** Alpha-2-macroglobulin is a protease inhibitor and is one of the largest plasma proteins. It transports hormones and enzymes, exhibits effector and inhibitor functions in the development of the lymphatic system, and inhibits components of the complement system and hemostasis system. Increased levels of alpha-2-macroglobulin are found in nephrotic syndrome when other lower molecular weight proteins are lost and alpha-2-macroglobulin is retained because of its large size. In patients with liver cirrhosis and diabetes, the levels are found to be elevated. Patients with acute pancreatitis exhibit low serum concentrations, which correlate with the severity of the disease. In hyperfibrinolytic states, after major surgery, in septicemia, and severe hepatic insufficiency, the measured levels of alpha-2-macroglobulin are often low. Acute myocardial infarction patients with low alpha-2-macroglobulin have been reported to have a significantly better prognosis with regard to the greater than a year survival time.

**Useful For:** Evaluation of patients with nephrotic syndrome and pancreatitis

**Useful For:**
**Interpretation:** Values are elevated in the nephrotic syndrome in proportion to the severity of protein loss (lower molecular weight). Values are low in proteolytic diseases such as pancreatitis.

**Reference Values:**
- < or =18 years: 178-495 mg/dL
- >18 years: 100-280 mg/dL

**Clinical References:**

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**Alpha-Amylase, IgE, Serum**

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

**Useful For:** Establishing the diagnosis of an allergy Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
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<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
</tbody>
</table>
| > or =100     | Strongly positive Reference values apply to all ages.

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**ALFP**

**Alpha-Fetoprotein (AFP) Immunostain, Technical Component Only**

**Clinical Information:** Alpha-fetoprotein (AFP) is an oncofetal antigen normally expressed in fetal liver, but not present in normal adult tissues. AFP can be expressed in yolk sac tumors and in hepatocellular carcinomas.

**Useful For:** Aiding in the identification of yolk sac tumors and hepatocellular carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**L3AFP**

**Alpha-Fetoprotein (AFP) L3% and Total, Hepatocellular Carcinoma Tumor Marker, Serum**

**Clinical Information:** Worldwide, hepatocellular carcinoma is the third leading cause of death from cancer.(1) While hepatocellular carcinoma can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of suspected hepatocellular carcinoma. However, increased serum concentrations of AFP might be found in chronic hepatitis and liver cirrhosis as well as in other tumor types (eg, germ cell tumors),(2) decreasing the specificity of AFP testing for hepatocellular carcinoma. Furthermore, AFP is not expressed at high levels in all hepatocellular carcinoma patients, resulting in decreased sensitivity, especially in potentially curable small tumors. AFP is differentially glycosylated in several hepatic diseases. For example, uridine diphosphate (UDP)-alpha-(1->6)-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation. This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following electrophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP, which is most closely associated with hepatocellular carcinoma, is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP of 200 ng/mL or below, which may result from a variety of benign pathologies such as chronic liver diseases. AFP-L3 should be utilized as an adjunct to high-resolution ultrasound for surveillance of individuals at significant risk for developing hepatic lesions.

**Useful For:** Distinguishing between hepatocellular carcinoma and chronic liver disease Monitoring individuals with hepatic cirrhosis from any etiology for progression to hepatocellular carcinoma Surveillance for development of hepatocellular carcinoma in individuals with a positive family history of hepatic cancer Surveillance for development of hepatocellular carcinoma in individuals within specific...
ethnic and gender groups who do not have hepatic cirrhosis, but have a confirmed diagnosis of chronic infection by hepatitis B acquired early in life including: - African males above the age of 20 - Asian males above the age of 40 - Asian females above the age of 50

**Interpretation:** Alpha-fetoprotein (AFP)-L3 results of 10% or above are associated with a 7-fold increased risk of developing hepatocellular carcinoma. Patients with AFP-L3 at this level should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. A total serum AFP above 200 ng/mL is highly suggestive of a diagnosis of hepatocellular carcinoma. In patients with liver disease, a total serum AFP at this level is near 100% predictive of hepatocellular carcinoma. With decreasing total AFP levels, there is an increased likelihood that chronic liver disease, rather than hepatocellular carcinoma, is responsible for the AFP elevation. AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life.

**Reference Values:**
TOTAL AFP:  
<4.7 ng/mL%
L3:  
<10%


**Alpha-Fetoprotein (AFP) Tumor Marker, Serum**

**Clinical Information:** Alpha-fetoprotein (AFP) is a glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including hepatocellular carcinoma, hepatoblastoma, and nonseminomatous germ cell tumors of the ovary and testis (eg, yolk sac and embryonal carcinoma). Most studies report elevated AFP concentrations in approximately 70% of patients with hepatocellular carcinoma. Elevated AFP concentrations are found in 50% to 70% of patients with nonseminomatous testicular tumors.(1) AFP is elevated during pregnancy. Persistence of AFP in the mother following birth is a rare hereditary condition.(2) Neonates have markedly elevated AFP levels (>100,000 ng/mL) that rapidly fall to below 100 ng/mL by 150 days and gradually return to normal over their first year.(2) Concentrations of AFP above the reference range also have been found in the serum of patients with benign liver disease (eg, viral hepatitis, cirrhosis), gastrointestinal tract tumors, and along with carcinoembryonic antigen, in ataxia telangiectasia. The biological half-life of AFP is approximately 5 days.

**Useful For:** Follow-up management of patients undergoing cancer therapy, especially for testicular and ovarian tumors and for hepatocellular carcinoma Often used in conjunction with human chorionic gonadotropin.(2) This test is not recommended as a screening procedure for cancer detection in the general population. This test is not intended for the detection of neural tube defects. This test is not useful for patients with pure seminoma or dysgerminoma.

**Interpretation:** Alpha-fetoprotein (AFP) levels may be elevated in association with a variety of
malignancies or benign diseases. Failure of the AFP value to return to normal by approximately 1 month after surgery suggests the presence of residual tumor. Elevation of AFP after remission suggests tumor recurrence; however, tumors originally producing AFP may recur without an increase in AFP.

**Reference Values:**

<8.4 ng/mL

Reference values are for nonpregnant subjects only; fetal production of AFP elevates values in pregnant women.

Range for newborns is not available, but concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 months of life. (See literature reference: Ped Res 1981;15:50-52) For further interpretive information, see Alpha-Fetoprotein (AFP) in Special Instructions.

Serum markers are not specific for malignancy, and values may vary by method.

**Clinical References:**


**Alpha-Fetoprotein (AFP), Peritoneal Fluid**

**Clinical Information:** Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Alpha-fetoprotein (AFP) measurement in serum is used in the management of patients with hepatocellular carcinoma (HCC). Measurement of AFP in ascites fluid might be useful, when used in conjunction with cytology, in patients with a history of HCC and in whom a cause of peritoneal fluid accumulation is uncertain.

**Useful For:** An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

**Interpretation:** A peritoneal fluid alpha-fetoprotein (AFP) concentration >6.0 ng/mL is suspicious but not diagnostic of ascites related to hepatocellular carcinoma (HCC). This clinical decision limit cutoff yielded a sensitivity of 58%, specificity of 96% in a study of 137 patients presenting with ascites. AFP concentrations were significantly higher in ascites caused by HCC. Ascites caused by malignancies other than HCC routinely had AFP concentrations <6.0 ng/mL. Therefore, negative results should be interpreted with caution.

**Reference Values:**

An interpretive report will be provided.

Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum

Clinical Information: Alpha-fetoprotein (AFP) is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from the nonpregnancy level of 0.2 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect (NTD), AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal distress situations (eg, threatened abortion and fetal demise) also may result in maternal serum AFP elevations. Increased maternal serum AFP concentrations also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP concentrations have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18 (Edwards syndrome). Risks for these syndrome disorders are only provided with the use of multiple marker screening (QUAD1 / Quad Screen [Second Trimester] Maternal, Serum). Measurement of maternal serum AFP values is a standard tool used in obstetrical care to identify pregnancies that may have an increased risk for NTD. The screen is performed by measuring AFP in maternal serum and comparing this value to the median AFP value in an unaffected population to obtain a multiple of the median (MoM). The laboratory has established a MoM cutoff of 2.5, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered.

Useful For: Prenatal screening for open neural tube defect

Interpretation: Neural tube defects A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of neural tube defects (NTD). A screen-positive result indicates that the calculated AFP MoM is 2.50 or greater and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual’s pretest risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with an open NTD have elevated AFP MoM values greater than 2.50. Follow up: Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (ie, weight, diabetic status, gestational dating). If any information is incorrect the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD screen-positive results. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTD) are typically offered.

Reference Values: NEURAL TUBE DEFECTS

An AFP multiple of the median (MoM) <2.5 is reported as screen negative.

AFP MoMs > or ≈2.5 (singleton and twin pregnancies) are reported as screen positive.

An interpretive report will be provided.

Alpha-Fetoprotein (AFP), Spinal Fluid

Clinical Information: Alpha-fetoprotein (AFP) is an oncofetal glycoprotein, homologous with albumin that is produced both in early fetal life and in tumors arising from midline embryonic structures. AFP is synthesized in the yolk sac, liver, and gastrointestinal track of the fetus. In adults, the liver synthesizes AFP. AFP is not normally expressed in the central nervous system (CNS). AFP levels in liver are increased in hepatomas and hepatocellular and colon carcinomas, as well as in germ-cell tumors arising from the ovaries and nonseminomatomous germ-cell tumors of the testes, testicular teratocarcinomas, and primary germ-cell tumors arising within the CNS. The presence of germinomas in the CNS and CNS involvement in metastatic cancer and meningeal carcinomatosis results in increased levels of AFP in cerebrospinal fluid.

Useful For: An adjunct in the diagnosis of central nervous system (CNS) germinomas and meningeal carcinomatosis Evaluating germ-cell tumors, including testicular cancer metastatic to the CNS in conjunction with beta-human chorionic gonadotropin measurement(1) An adjunct in distinguishing between suprasellar dysgerminomas and craniopharyngiomas A supplement to cerebrospinal fluid cytologic analysis

Interpretation: Alpha-fetoprotein (AFP) concentrations that exceed the upper end of normal are consistent with the presence of central nervous system germinoma, meningeal carcinomatosis, or metastatic nonseminomatosus testicular cancer. AFP is not elevated in the presence of a craniopharyngioma.

Reference Values:
<1.5 ng/mL

Values for alpha-fetoprotein in cerebrospinal fluid have not been formally established for newborns and infants. The available literature indicates that by 2 months of age, levels comparable to adults should be reached.(Ann Clin Biochem 2005;42:24-29)


Alpha-Fetoprotein, Amniotic Fluid

Clinical Information: Alpha-fetoprotein (AFP) is a single polypeptide chain glycoprotein with a molecular weight of approximately 70,000 Da. Synthesis of AFP occurs primarily in the liver and yolk sac of the fetus. It is secreted in fetal serum, reaching a peak at approximately 13 weeks gestation, after which it rapidly declines until about 22 weeks gestation and then gradually declines until term. Transfer of AFP into maternal circulation is accomplished primarily through diffusion across the placenta. Maternal serum AFP levels rise from the normal non-pregnancy level of 0.20 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Other fetal abnormalities such as omphalocoele, gastrochisis, congenital renal disease, and esophageal atresia; and other fetal distress situations such as threatened abortion, prematurity, and fetal demise, may also show AFP elevations. Decreased amniotic fluid AFP values may be seen when gestational age has been overestimated.

Useful For: Screening for open neural tube defects or other fetal abnormalities Follow-up testing for
patients with elevated serum alpha-fetoprotein results or in conjunction with cytogenetic testing

**Interpretation:** A diagnostic alpha-fetoprotein (AFP) cutoff level of 2.0 multiples of median (MoM), followed by acetylcholinesterase (AChE) confirmatory testing on positive results, is capable of detecting 96% of open spina bifida cases with a false-positive rate of only 0.06% in nonblood-stained specimens. AChE analysis is an essential confirmatory test for all amniotic fluid specimens with positive AFP results. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of open communication between fetal central nervous system (eg, open neural tube defects), or to a lesser degree, fetal circulation. All amniotic fluid specimens testing positive for AFP will have the AChE test performed. False-positive AChE may occur from a bloody tap, which may cause both elevated AFP and AChE levels.

**Reference Values:**
< or = 2.0 multiples of median (MoM)

**Clinical References:**

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**FUCW 8814**

**Alpha-Fucosidase, Leukocytes**

**Clinical Information:** Fucosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent alpha-L-fucosidase enzyme activity. This enzyme is involved in degrading asparagine-linked, fucose-containing complex molecules (oligosaccharides and glycoasparagines) present in cells. Reduced or absent activity of this enzyme results in the abnormal accumulation of these molecules in the tissues and body fluids. Severe and mild subgroups of fucosidosis, designated types I and II, have been described, although recent data suggests individual patients may represent a continuum within a wide spectrum of severity. The more severe type is characterized by infantile onset, rapid psychomotor regression, and severe neurologic deterioration. Additionally, dysostosis multiplex and elevated sweat sodium chloride are frequent findings. Death typically occurs within the first decade of life. Those with the milder phenotype express comparatively mild psychomotor and neurologic regression, radiologic signs of dysostosis multiplex and skin lesions (angiokeratoma corporis diffusum). Normal sweat salinity, the presence of the skin lesions, and survival into adulthood most readily distinguish milder from more severe phenotypes. Although the disorder is panethnic, the majority of reported patients with fucosidosis have been from Italy and southwestern United States. To date, about 100 cases have been reported worldwide. An initial diagnostic workup includes a urine screening assay for several oligosaccharidosis (OLIGU / Oligosaccharide Screen, Random, Urine). If the screening assay is suggestive of fucosidosis, enzyme analysis of alpha-L-fucosidase can confirm the diagnosis.

**Useful For:** Detection of fucosidosis This test is not useful for establishing carrier status for fucosidosis.

**Interpretation:** Values below 0.32 nmol/min/mg protein are consistent with a diagnosis of fucosidosis.

**Reference Values:**
> or = 0.32 nmol/min/mg protein

**Clinical References:**
**Alpha-Galactosidase, Blood Spot**

**Clinical Information:** Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body, in particular, the kidney, heart, and brain. Variants within the GLA gene cause Fabry disease with severity and symptom onset dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to end-stage renal disease (ESRD) typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Measurement of alpha-Gal A in blood spots, leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can reliably diagnose classic or variant Fabry disease in males. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with ESRD but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for confirmation of a diagnosis of classic or variant Fabry disease in affected male patients with reduced alpha-Gal A activity. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals will have normal levels. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended as the most appropriate diagnostic test to detect asymptomatic or symptomatic female carriers. The biomarkers globotriaosylsphingosine (LGB3S / Globotriaosylsphingosine, Serum) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in patients with Fabry disease and can also be used in follow up of absent or reduced alpha-Gal A activity in both male and female patients. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. In addition, some (adult) patients may be candidates for an oral chaperone therapy. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented. Molecular genetic testing is the recommended diagnostic test for female patients as alpha-Gal A may be in the normal range in an affected female patient.

**Useful For:** Diagnosis of Fabry disease in male patients using blood spot specimens Verifying abnormal serum alpha-galactosidase results in male patients with a clinical presentation suggestive of Fabry disease Follow-up to an abnormal newborn screen for Fabry disease This test is not useful for patients undergoing a workup for a meat or meat-derived product allergy.

**Interpretation:** In male patients, results less than 1.2 nmol/mL/hour in properly submitted specimens are consistent with Fabry disease. Normal results (> or =1.2 nmol/mL/hour) are not consistent with Fabry disease. In female patients, normal results (> or =2.8 nmol/mL/hour) in properly submitted specimens are typically not consistent with carrier status for Fabry disease; however, enzyme analysis, in general, is not sufficiently sensitive to detect all carriers. Because a carrier range has not been established in females, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) should be considered when alpha-galactosidase A activity is less than 2.9 nmol/mL/hour, or if clinically indicated. Pseudodeficiency results in low measured alpha-galactosidase A activity but is not consistent with Fabry disease; FABRZ / Fabry Disease, Full Gene Analysis, Varies should be performed to resolve the clinical question. See Fabry Disease Diagnostic Testing Algorithm in Special Instructions.

**Reference Values:**
- Males: > or =1.2 nmol/mL/hour
- Females: > or =2.8 nmol/mL/hour

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An interpretive report will be provided.

**Clinical References:**

**Alpha-Galactosidase, Leukocytes**

**Clinical Information:** Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body, in particular, in the kidney, heart, and brain. Alterations within the GLA gene cause Fabry disease and more than 630 genetic alterations have been identified. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiookeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to end-stage renal disease (ESRD) typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with ESRD but without the pain or skin lesions; a cardiac variant typically presenting in the 6th to 8th decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected.

Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals will have normal levels. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended as the most appropriate diagnostic test to detect carriers. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. In addition, some adult patients may be candidates for an oral chaperone therapy. For this reason, early diagnosis and treatment are desirable and, in a few US states, early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots (AGABS / Alpha-Galactosidase, Blood Spot), leukocytes (this test), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. The biomarkers globotriaosylsphingosine (LGBWB / Globotriaosylsphingosine, Blood) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in patients with Fabry disease and may aid in the diagnostic evaluation of females. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in both male and female patients.

**Useful For:** Diagnosis of Fabry disease in male patients Verifying abnormal serum alpha-galactosidase results in male patients with a clinical presentation suggestive of Fabry disease This test is not useful for patients undergoing a work-up for a meat or meat-derived product allergy.

**Interpretation:** Values below the reference range are consistent with a diagnosis Fabry Disease. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro, confirmatory studies.
Reference Values:
> or =10.32 nmol/hour/mg protein
An interpretative report will be provided.

Note: Results from this assay do not reflect carrier status because of individual variation of alpha-galactosidase enzyme levels.

**Clinical References:**

**Alpha-Galactosidase, Serum**

**Clinical Information:** Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body; in particular, in the kidney, heart, and brain. Variants within the GLA gene cause Fabry disease and more than 630 variants have been identified. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to end-stage renal disease (ESRD) typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with ESRD but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended to detect carriers. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. In addition, some (adult) patients may be candidates for an oral chaperone therapy. For this reason, early diagnosis and treatment are desirable, and in a few US states, early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots (AGABS / Alpha-Galactosidase, Blood Spot), leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in both male and female patients. The biomarkers globotriaosylsphingosine (LGB3S / Globotriosylsphingosine, Serum) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) are typically elevated in symptomatic patients with Fabry disease and may aid
in the diagnostic evaluation of female patients and in individuals with a variant of uncertain significance in GLA. See Fabry Disease Testing Algorithm and Fabry Disease: Newborn Screen-Positive Follow-up in Special Instructions.

**Useful For:** Diagnosis of Fabry disease in male patients Preferred screening test (serum) for Fabry disease This test is not useful for patients undergoing a work up for a meat or meat-derived product allergy.

**Interpretation:** Deficiency (<0.016 U/L) of alpha-galactosidase in properly submitted specimens is diagnostic for Fabry disease in male patients. If concerned about specimen integrity, recheck using leukocyte testing (AGAW / Alpha-Galactosidase, Leukocytes).

**Reference Values:**
0.074-0.457 U/L

Note: Results from this assay are not useful for carrier determination. Carriers usually have levels in the normal range.

**Clinical References:**

**ATHL 58114**

**Alpha-Globin Gene Analysis**

**Reference Values:**
Only orderable as part of a profile. For more information see ATHAL / Alpha-Globin Gene Analysis.

**ATHAL 35346**

**Alpha-Globin Gene Analysis, Varies**

**Clinical Information:** The thalassemias are a group of inherited conditions characterized by decreased synthesis of one or more of the globin chains, resulting in an imbalance in the relative amounts of the alpha and beta chains. The excess normal chains precipitate in the cell, damaging the membrane and leading to premature red blood cell destruction. Additionally, the defect in hemoglobin synthesis produces a hypochromic, microcytic anemia. The frequency of the thalassemias is due to the protective advantage against malaria that it gives carriers. Consequently, thalassemias are prevalent in populations from equatorial regions in the world where malaria is endemic. Alpha-thalassemia is caused by decreased synthesis of alpha-globin chains. Four alpha-globin genes are normally present (2 on each chromosome 16). One, 2, 3, or 4 alpha-globin genes may be deleted or, less commonly, contain variants. Deletions account for approximately 90% of disease-causing alleles in alpha thalassemia. Phenotypically, these deletions result in 4 categories of disease expression: -Deletion of 1 alpha-chain: Silent carrier state, with a normal phenotype -Deletion of 2 alpha-chains: Alpha-thalassemia trait (alpha-1 thalassemia), with mild hematologic changes but no major clinical difficulties -Deletion of 3 alpha-chains: Hemoglobin H disease, which is extremely variable but usually includes anemia due to hemolysis, jaundice, and hepatosplenomegaly -Deletion of all 4 alpha-chains: Hemoglobin Bart, with hydrops fetalis and almost invariably in utero demise Less frequently, alpha-thalassemia results from single point alterations, such as hemoglobin Constant Spring (HbCS) (HBA2: c.427T >C). Note: these point alterations are not detected by this assay. Alpha-thalassemia occurs in all ethnic groups but is
especially common individuals of Southeast Asian and African ancestry. It is also frequent in individuals of Mediterranean ancestry. The carrier frequency is estimated to be 1 in 20 for Southeast Asians, 1 in 30 for African Americans, and 1 in 30 to 1 in 50 for individuals of Mediterranean ancestry. Both deletional and nondeletional (caused by point alterations) forms of alpha-thalassemia are found in individuals with Mediterranean ancestry. Deletions in cis (deletions on the same chromosome) are rare in African or Mediterranean populations but are prevalent in Asian populations. Couples in which both partners carry deletions in cis are at risk of having a child with the fatal hemoglobin Bart hydrops fetalis syndrome.

**Useful For:** Diagnosis of alpha-thalassemia Prenatal diagnosis of deletional alpha-thalassemia Carrier screening for individuals from high-risk populations for alpha-thalassemia This test is not useful for diagnosis or confirmation of beta-thalassemia or hemoglobinopathies.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Alpha-L-Iduronidase, Leukocytes**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate, also known as glycosaminoglycans (GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG. MPS disorders involve multiple organ systems and are characterized by coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Individuals with MPS I typically demonstrate elevated urinary levels of the GAG dermatan sulfate and heparan sulfate (see MPSSC / Mucopolysaccharides Screen, Random, Urine; MPSWB / Mucopolysaccharides, Blood). Reduced or absent activity of alpha L-iduronidase can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene allows for detection of a disease-causing variant in affected individuals and subsequent carrier detection in relatives (see MPS1Z / Hurler Syndrome, Full Gene Analysis, Varies). To date, a clear genotype-phenotype correlation has not been established.

**Useful For:** Diagnosis of mucopolysaccharidosis I, Hurler, Scheie, and Hurler-Scheie syndromes in leukocytes This test is not useful for determining carrier status.

**Interpretation:** Results below 2.06 nmol/hour/mg protein in properly submitted specimens are consistent with alpha-L-iduronidase deficiency (mucopolysaccharidosis I). Further differentiation between
Hurler, Scheie, and Hurler-Scheie syndromes is dependent upon the clinical findings. Normal results (> or =2.06 nmol/hour/mg protein) are not consistent with alpha-L-iduronidase deficiency.

**Reference Values:**
- > or =2.06 nmol/hour/mg protein

An interpretive report will be provided.

**Clinical References:**

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**Alpha-Lactalbumin, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to alpha-lactalbumin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
5  Strongly positive

6  > or =100  Strongly positive  Reference values apply to all ages.


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**MANN 62511  Alpha-Mannosidase, Leukocytes**

**Clinical Information:** Alpha-mannosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid alpha-mannosidase enzyme activity. This enzyme is involved in glycoprotein catabolism, with absent or reduced activity resulting in the accumulation of undigested mannose-containing complex oligosaccharides in the lysosomes, disrupting the normal functioning of cells. Clinical features and severity of symptoms are widely variable within alpha-mannosidosis but, in general, the disorder is characterized by skeletal abnormalities, immune deficiency, hearing impairment, and mental retardation. Three clinical subtypes of the disorder have been described and vary with respect to age of onset and clinical presentation. Type 1 is generally classified by a mild presentation and slow progression with onset after 10 years of age and absence of skeletal abnormalities. Type 2 is generally a more moderate form with slow progression and onset prior to 10 years of age with skeletal abnormalities and myopathy. Type 3 is the most severe form with onset in early infancy, skeletal abnormalities such as dysostosis multiplex, and severe central nervous system involvement. Although treatment is mostly supportive and aimed at preventing complications, hematopoietic stem cell transplant has been reported to be a feasible therapeutic option. The incidence of alpha-mannosidosis is estimated at 1 in 500,000 live births. An initial diagnostic workup may include a screening assay for several oligosaccharides in urine, OLIGU / Oligosaccharide Screen, Random, Urine. If the urine oligosaccharide screening assay is suggestive of alpha-mannosidosis, enzyme analysis of acid alpha-mannosidase can confirm the diagnosis.

**Useful For:** Diagnosis of alpha-mannosidosis  This test is not useful for establishing carrier status for alpha-mannosidosis.

**Interpretation:** Values below 0.54 nmol/min/mg protein are consistent with a diagnosis of alpha-mannosidosis.

**Reference Values:** > or =0.54 nmol/min/mg protein


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**ANAS 8782  Alpha-N-Acetylglucosaminidase, Serum**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Sanfilippo syndrome (MPS type III) is an autosomal recessive MPS with 4 recognized types (A-D). Each type is caused by a deficiency in 1 of 4 enzymes involved in the
degradation of heparan sulfate resulting in its lysosomal accumulation. Though biochemically different, the clinical presentation of all types is indistinguishable. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but other symptoms seen in MPS, such as coarse facial features and skeletal involvement, tend to be milder. Onset of clinical features usually occurs between 2 and 6 years in a child who previously appeared normal. The presenting symptoms are most commonly developmental delay and severe behavioral problems. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by age 20, although individuals with an attenuated phenotype may have a longer life expectancy and remain functional into their third and fourth decades. Sanfilippo syndrome type B is due to a deficiency of the enzyme N-acetyl-alpha-D-glucosaminidase (alpha-hexosaminidase), caused by variants in the NAGLU gene. Affected individuals demonstrate elevations of heparan sulfate in blood and urine (MPSBS / Mucopolysaccharosis, Blood Spot and MPSQU/ Mucopolysaccharides Quantitative, Random, Urine). Diagnostic sequencing of the NAGLU gene (MP3BZ / Mucopolysaccharidoses IIIB, Full Gene Analysis, Varies) and deletion/duplication studies are available for patients with an enzyme deficiency. Elevations in serum of alpha-N-acetylgalactosaminidase and other hydrolases may be seen in patients with mucolipidosis II/III (I-cell disease).(1) I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylgalactosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of alpha-N-acetylgalactosaminidase activity is not the preferred diagnostic test for I-cell disease but may be included in the testing strategy.

**Useful For:** Diagnosis of Sanfilippo syndrome type B (mucopolysaccharidoses type IIIB) This test is not suitable for carrier detection.

**Interpretation:** Deficiency of alpha-N-acetylgalactosaminidase is diagnostic for Sanfilippo syndrome type B.

**Reference Values:**
0.09-0.58 U/L

**Clinical References:**
less homology, and convey the receptor specificity of the dimeric hormones. Under physiological conditions, alpha- and beta-chain synthesis and secretions are tightly coupled, and only small amounts of monomeric subunits are secreted. However, under certain conditions, coordinated production of intact glycoprotein hormones may be disturbed and disproportionate quantities of free alpha-subunits are secreted. In particular, some pituitary adenomas may overproduce alpha-subunits. Although most commonly associated with gonadotroph- or thyrotroph-derived tumors, alpha-subunit secretion has also been observed in corticotroph, lactotroph, and somatotroph pituitary adenomas. Overall, depending on cell type and tumor size, 5% to 30% of pituitary adenomas will produce sufficient free alpha-subunits to result in elevated serum levels, which usually fall with successful treatment. Stimulation testing with hypothalamic releasing factors (eg, gonadotropin releasing hormone: GnRH or thyrotropin-releasing hormone: TRH) may result in further elevations, disproportionate to those seen in individuals without tumors. Measurement of free alpha-subunit after GnRH-stimulation testing can also be useful in the differential diagnosis of constitutional delay of puberty (CDP) versus hypogonadotrophic hypogonadism (HH). CDP is a benign, often familial, condition in which puberty onset is significantly delayed, but eventually occurs and then proceeds normally. By contrast, HH represents a disease state characterized by lack of gonadotropin production. Its causes are varied, including hypothalamic and pituitary inflammatory or neoplastic disorders, a range of specific genetic abnormalities, as well as unknown causes. In children, HH results in complete failure to enter puberty without medical intervention. In children with CDP, in normal pubertal children, in normal adults and, to a lesser degree, in normal prepubertal children, GnRH administration results in increased serum LH, FSH, and alpha-subunit levels. This response is greatly attenuated in patients with HH, particularly with regard to the post-GnRH rise in alpha-subunit concentrations.

**Useful For:** Adjunct in the diagnosis of pituitary tumors As part of the follow-up of treated pituitary tumor patients Differential diagnosis of thyrotropin-secreting pituitary tumor versus thyroid hormone resistance Differential diagnosis of constitutional delay of puberty versus hypogonadotrophic hypogonadism

**Interpretation:** In the case of pituitary adenomas that do not produce significant amounts of intact tropic hormones, diagnostic differentiation between sellar- and tumors of non-pituitary origin (eg, meningeomas or craniopharyngiomas) can be difficult. In addition, if such nonsecreting adenomas are very small, they can be difficult to distinguish from physiological pituitary enlargements. In a proportion of these cases, free alpha-subunit may be elevated, aiding in diagnosis. Overall, 5% to 30% of pituitary adenomas produce measurable elevation in serum free alpha-subunit concentrations. There is also evidence that an exuberant free alpha-subunit response to thyrotropin-releasing hormone (TRH) administration may occur in some pituitary adenoma patients that do not have elevated baseline free alpha-subunit levels. A more than 2-fold increase in free alpha-subunit serum concentrations at 30 to 60 minutes following intravenous administration of 500 mcg of TRH is generally considered abnormal, but some investigators consider any increase of serum free alpha-subunit that exceeds the reference range as abnormal. TRH testing is not performed in the laboratory but in specialized clinical testing units under the supervision of a physician. In pituitary tumors patients with pre-treatment elevations of serum free alpha-subunit, successful treatment is associated with a reduction of serum free alpha-subunit levels. Failure to lower levels into the normal reference range may indicate incomplete cure, and secondary rises in serum free alpha-subunit levels can indicate tumor recurrence. Small thyrotropin (TSH)-secreting pituitary tumors are difficult to distinguish from thyroid hormone resistance. Both types of patients may appear clinically euthyroid or mildly hyperthyroid and may have mild-to-modest elevations in peripheral thyroid hormone levels along with inappropriately (for the thyroid hormone level) detectable TSH, or mildly-to-modestly elevated TSH. Elevated serum free alpha-subunit levels in such patients suggest a TSH secreting tumor, but genetic variant screening of the thyroid hormone receptor gene may be necessary for a definitive diagnosis. Constitutional delay of puberty (CDP), is a benign, often familial condition, in which puberty onset is significantly delayed, but eventually occurs and then proceeds normally. By contrast, hypogonadotrophic hypogonadism (HH) represents a disease state characterized by lack of gonadotropin production. Its causes are varied, ranging from idiopathic over specific genetic abnormalities to hypothalamic and pituitary inflammatory or neoplastic disorders. In children, it results in complete failure to enter puberty without medical intervention. CDP and HH can be extremely difficult to distinguish from each other. Intravenous administration of 100 mcg gonadotropin releasing hormone (GnRH) results in much more substantial rise in free alpha-subunit levels in CDP patients, compared with HH patients. A greater than 6-fold rise at 30 or 60 minutes post-injection is seen in more than 75% of
CDP patients, while a less than 2-fold rise appears diagnostic of HH. Increments between 2- and 6-fold are nondiagnostic. GnRH testing is not performed in the laboratory but in specialized clinical testing units under the supervision of a physician.

**Reference Values:**

**PEDIATRIC**

< or =5 days: < or =50 ng/mL  
6 days-12 weeks: < or =10 ng/mL  
3 months-17 years: < or =1.2 ng/mL  
Tanner II-IV*: < or =1.2 ng/mL

**ADULTS**

Males: < or =0.5 ng/mL  
Premenopausal females: < or =1.2 ng/mL  
Postmenopausal females: < or =1.8 ng/mL

Pediatric and adult reference values based on Mayo studies.

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

**Clinical References:**

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**Alpha/Beta Crystallin IHC, Technical Component Only**

**Clinical Information:** Alpha-beta crystallin is a lens protein and a member of the superfamily of small heat shock proteins. It is expressed in a variety of tissues such as skeletal muscle, cardiac muscle, smooth muscle, renal tubular epithelium, Schwann cells, glial cells, thyroid epithelium, colonic epithelium, and stratified squamous epithelium. It is also found in ubiquitinated intermediate filament inclusion bodies, such as Lewy bodies (neurofilaments), Rosenthal fibers (glial filaments), and Mallory bodies (cytokeratins) present in certain disease states.

**Useful For:** Characterization of neuroectodermal tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**  

**ALPRT**  
**Alport (Collagen IV Alpha 5 and Alpha 2) Immunofluorescent Stain, Renal Biopsy**

**Clinical Information:** Alport syndrome is a hereditary disease of basement membrane collagen type IV. Variants in collagen IV alpha genes cause characteristic abnormal immunofluorescence staining patterns within the glomerular basement membrane. Alport syndrome is characterized by hematuria, proteinuria, progressive renal failure, and high-tone sensorineural hearing loss.

**Useful For:** Assisting in the diagnosis of hereditary nephritis (Alport syndrome)

**Interpretation:** This test, (when not accompanied by a pathology consultation request) will be reported as: 1) normal pattern, 2) consistent with X-linked hereditary nephritis, or 3) consistent with autosomal hereditary nephritis. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.

**Reference Values:**  
An interpretive report will be provided.


**FALPX**  
**Alprazolam (Xanax)**

**Reference Values:**  
5 Âµg/mL  25 ng/mL

**Reporting Limit:** 2.0 ng/mL

**ALTN**  
**Alternaria tenuis, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Alternaria tenuis Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>Positive</td>
</tr>
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<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

grouping of complement conditions where there is loss of control of the complement cascade with over-activation. In several cases, the complement system will attack the host and the over-activation of the complement cascade may cause disease. Over-activation of the alternative pathway usually presents with renal function impairment, in rare conditions such as atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathies (dense deposit disease [DDD] and C3 glomerulonephritis [C3GN]). The use of complement inhibitor therapies such as eculizumab and ravulizumab will result in the blocking of C5. C5 is necessary for the AH50 test to progress until the formation of the MAC. Hence, in the presence of eculizumab or ravulizumab, AH50 results will be decreased or undetectable.

**Useful For:** Investigation of suspected alternative pathway complement deficiency, atypical hemolytic uremic syndrome, C3 glomerulonephritis, dense-deposit disease

**Interpretation:** Absent complement alternative pathway (AH50) in the presence of a normal total hemolytic complement (CH50) suggests an alternative pathway component deficiency. Normal AH50 with absent CH50 suggests an early (C1, C2, C4) classic pathway deficiency. Absent AH50 and CH50 suggests a late (C3, C5, C6, C7, C8, C9) component deficiency or complement consumption. Absent AH50 and CH50 in the presence of a normal C3 and C4 suggests a late (C5, C6, C7, C8, C9) component deficiency. Normal CH50 and AH50 in the presence of recurrent infection and continued suspicion of complement deficiency, suggest testing for lectin pathway function.

**Reference Values:**
> or =46% normal

**Clinical References:**

**Aluminum, 24 Hour, Urine**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in RF patients: - Aluminum-laden dialysis water can expose dialysis patients to aluminum. - Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. - The dialysis process is not highly effective at eliminating aluminum. - Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring aluminum exposure Preferred matrix for assessment of exposure in patients with normal renal function since rapidly filtered by kidneys Monitoring metallic prosthetic implant wear This test is not an acceptable substitute for serum aluminum measurements and is not recommended for routine aluminum screening.
**Interpretation:** Daily excretion greater than 10 mcg/24 hours indicates exposure to excessive amounts of aluminum. In renal failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal. Prosthesis wear is known to result in increased circulating concentration of metal ions. (1,2) Modest increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations above 50 mcg/24 hours in a patient with an aluminum-based implant and not undergoing dialysis, suggests significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**

- 0-17 years: not established
- > or =18 years: <10 mcg/24 hours

**Clinical References:**

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**Aluminum, Serum**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in patients in RF: -Aluminum-laden dialysis water can expose dialysis patients to aluminum.
- Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Deposition of aluminum in bone also interrupts normal calcium exchange. The calcium in bone becomes unavailable for resorption back into blood under the physiologic control of parathyroid hormone (PTH) and results in secondary hyperparathyroidism. While PTH is typically quite elevated in RF, 2 different processes may occur: 1) High-turnover bone disease associated with high PTH (>150 pg/mL) and relatively low aluminum (<20 ng/mL), or 2) low-turnover bone disease with lower PTH (<50 pg/mL) and high aluminum (>60 ng/mL). Low-turnover bone disease indicates aluminum intoxication. Serum aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Preferred monitoring for aluminum toxicity in patients undergoing dialysis Preferred test for routine aluminum screening Monitoring metallic prosthetic implant wear

**Interpretation:** Patients in renal failure not receiving dialysis therapy invariably have serum aluminum levels above the 60 ng/mL range. McCarthy(1) and Hernandez(2) describe a biochemical profile that is characteristic of aluminum overload disease in dialysis patients: -Patients in renal failure
with no signs or symptoms of osteomalacia or encephalopathy usually had serum aluminum below 20 ng/mL and parathyroid hormone (PTH) concentrations above 150 pg/mL, which is typical of secondary hyperparathyroidism. Patients with signs and symptoms of osteomalacia or encephalopathy had serum aluminum above 60 ng/mL and PTH concentrations below 50 pg/mL (PTH above the reference range, but low for secondary hyperparathyroidism). Patients who had serum aluminum above 60 ng/mL and below 100 ng/mL were identified as candidates for later onset of aluminum-overload disease that required aggressive efforts to reduce their daily aluminum exposure. This was done by switching them from aluminum-containing phosphate binders to calcium-containing phosphate binders, by ensuring that their dialysis water had less than 10 ng/mL of aluminum, and ensuring the albumin used during postdialysis therapy was aluminum free. Prosthesis wear is known to result in increased circulating concentration of metal ions.(3) Modest increase (6-10 ng/mL) in serum aluminum concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with an aluminum-based implant not undergoing dialysis suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:

0-6 ng/mL (all ages)
<60 ng/mL (dialysis patients-all ages)

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

Clinical References:
doi: 10.1111/hdi.12231

**ALCRU**

**Aluminum/Creatinine Ratio, Random, Urine**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in RF patients: -Aluminum-laden dialysis water can expose dialysis patients to aluminum. -Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring aluminum exposure when a 24-hour urine cannot be collected Monitoring metallic prosthetic implant wear when a 24-hour urine cannot be collected This test is not an acceptable substitute for serum aluminum measurements and is not recommended for routine aluminum screening.
Interpretation: Daily excretion more than 10 mcg/24 hours indicates exposure to aluminum. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations more than 50 mcg/24 hours in a patient with an aluminum-based implant, not undergoing dialysis, suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. In renal failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal.

Reference Values:

0-17 years: not established
> or =18 years: <14 mcg/g Creatinine


FOXOF 35281

Alveolar Rhabdomyosarcoma (ARMS), 13q14 (FOXO1 or FKHR) Rearrangement, FISH, Tissue

Clinical Information: Rhabdomyosarcomas are a heterogeneous group of malignant tumors showing skeletal muscle differentiation. They can be divided into 3 subtypes: alveolar, embryonal, and pleomorphic. The rarer alveolar rhabdomyosarcomas (ARMS) are seen in older children, are more likely to occur in limbs, and are associated with higher stage disease and an unfavorable prognosis. The alveolar form consists of 2 variants; classic and solid. The classic form is characterized by small round cells with dark hyperchromatic nuclei containing distinct nucleoli, held together by strands of intercellular collagen, thereby creating a cellular architecture resembling the alveolar spaces of the lungs. The solid form is characterized by a similar cellular morphology but without the formation of alveolar spaces. ARMS are also members of the small round cell tumor group that includes synovial sarcoma, lymphoma, Wilms tumor, Ewing sarcoma, and desmoplastic small round cell tumor. Most cases of ARMS (75%) are associated with a t(2;13)(q35;q14), where a chimeric gene is formed from the rearrangement of the PAX3 gene on chromosome 2 and the FOXO1(FKHR) gene on chromosome 13. A small subset of ARMS patients (10%) are associated with a variant translocation, t(1;13)(q36;q14), involving the PAX7 gene of chromosome 1 and the FOXO1 gene. Detection of these transcripts by RT-PCR (ARMS / Alveolar Rhabdomyosarcoma by Reverse Transcriptase PCR [RT-PCR]), which allows specific identification of the t(2;13) and t(1;13), has greatly facilitated the diagnosis of ARMS tumors. FISH analysis (using the FOXO1 probe) adds the ability to detect variant FOXO1 rearrangements not detectible by PCR, and will often yield results when the quality of the available RNA is poor or the PCR results are equivocal.

Useful For: Supporting the diagnosis of alveolar rhabdomyosarcomas (ARMS) when used in conjunction with an anatomic pathology consultation Aiding in the diagnosis of ARMS when reverse transcriptase-PCR results are equivocal or do not support the clinical picture

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FOXO1 FISH probe. A positive result suggests rearrangement of the FOXO1 gene region at 13q14 and is consistent with a subset of alveolar rhabdomyosarcomas (ARMS). A negative result suggests FOXO1 gene rearrangement is not present, but does not exclude the diagnosis of alveolar rhabdomyosarcomas (ARMS).

Reference Values:

An interpretive report will be provided.
**Clinical References:**


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**TFE3F 35319**

**Alveolar Soft Part Sarcoma (ASPS)/Renal Cell Carcinoma (RCC), Xp11.23 (TFE3), FISH, Tissue**

**Clinical Information:** Alveolar soft-part sarcoma (ASPS) is a rare malignant tumor typically occurring in patients in their 20s to 30s within the muscle and deep tissues of the extremities. ASPS is slow growing and refractory to chemotherapy with a propensity to metastasize. Prolonged survival is possible even with metastasis, although the long-term disease-related mortality rate is high. ASPS is characterized by a translocation that results in fusion of TFE3 on chromosome Xp11.2 with ASPSCR1 (also called ASPL or RCC17) on chromosome 17q25.3. Both balanced and unbalanced forms (loss of the derivative X chromosome) of the translocation have been observed. Another tumor, a rare subset of papillary renal cell carcinoma (RCC) with a distinctive pathologic morphology, has rearrangements of TFE3 with ASPSCR1 or other fusion partner genes. This tumor predominantly affects children and young adults, presents at an advanced stage but with an indolent clinical course, and is a distinct entity in the World Health Organization classification. Typically a balanced form of the translocation is present in the RCC variant. An assay to detect rearrangement of TFE3 is useful to resolve diagnostic uncertainty in these tumor types, as immunohistochemistry for TFE3 is not reliable.

**Useful For:** An aid in the diagnosis of alveolar soft-part sarcoma or renal cell carcinoma variant when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of nuclei with the abnormality exceeds the established normal cutoff for the TFE3 probe set. A positive result of TFE3 rearrangement is consistent with a diagnosis of alveolar soft-part sarcoma (ASPS) or renal cell carcinoma (RCC) variant. A negative result suggests that TFE3 is not rearranged, but does not exclude the diagnosis of ASPS or RCC variant.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


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**ADEVL 607273**

**Alzheimer Disease Evaluation, Spinal Fluid**

**Clinical Information:** Currently the diagnosis of probable Alzheimer disease (AD) is made based on clinical symptoms, largely by the exclusion of other causes of dementia, with postmortem evidence of AD pathology required to confirm the diagnosis. Two common neuropathologic features found in the brain of patients with AD dementia are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. These 2 groups of molecules are the most established biomarkers of the disease used in clinical
and research practice. Positron emission tomography (PET) imaging using FDA-approved amyloid radiotracer to visualize the presence of amyloid lesions in the cerebral cortex is available in some specialized centers. Measuring Abeta peptides and Tau proteins in cerebrospinal fluid (CSF) is being proposed as an alternative/adjunct to imaging studies to assess AD pathology. Recently the use of these biomarkers has been included in the new consensus research diagnostic criteria for AD, mild cognitive impairment (MCI), and preclinical AD, proposed by the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework. The CSF assays included in this evaluation are beta-amyloid (1-42; Abeta42), total-Tau (t-Tau) and phosphorylated-Tau (p-Tau181). Abeta42 is approximately 4 kDa protein of 42 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein (APP). Due to its hydrophobic nature, Abeta42 has the propensity to form aggregates and oligomers. Oligomers form fibrils that accumulate into amyloid plaques. These pathological changes in Abeta42 are reflected by the decrease in the CSF concentrations of Abeta42 and/or by the increase in the brain uptake of specific tracers during beta-amyloid PET. Tau is present as six isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-mRNA. The t-Tau assay measures all these isoforms. The most common post-translational modification of Tau proteins is phosphorylation. During neurodegeneration, abnormal phosphorylation leads to the formation of intracellular neurofibrillary tangles composed of the Tau protein that has undergone hyper-phosphorylation and developed aggregates of hyper-phosphorylated Tau proteins called p-Tau. The p-Tau assay detects phosphorylated Tau at threonine 181 (p-Tau181). Pathological changes associated with AD are reflected by an increase in the CSF concentrations of t-Tau and p-Tau. Increases in CSF t-Tau reflect the intensity of the neuronal and axonal damage and degeneration and is associated with a faster progression from MCI to AD. Increases in CSF p-Tau concentrations are also associated with a faster progression from MCI to AD with more rapid cognitive decline in AD patients and in mild AD dementia cases. The Alzheimer’s Association has developed an appropriate use criterion (AUC), in order to guide safe and optimal use of CSF testing for AD pathology detection in the diagnostic process. The use of CSF biomarker testing may be indicated for the following patient groups: 1) Patients with subjective cognitive decline (SCD) who are considered to be at increased risk for AD 2) Patients with MCI that is persistent, progressing, and unexplained 3) Patients with symptoms that suggest possible AD 4) MCI or dementia with an onset at an early age (less than 65) 5) Patients meeting core clinical criteria for probable AD with typical age of onset 6) Patients whose dominant symptom is a change in behavior (eg. Capgras syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression) and where AD diagnosis is being considered. Ultimately, the decision to initiate CSF testing for the evaluation of suspected AD is also based on the clinical judgment of expert providers and the patient’s individual presentation.

**Useful For:** Assessment of adults with cognitive impairment being evaluated for Alzheimer disease (AD) and other causes of cognitive impairment. These assays should not be used to predict the development of dementia or other neurologic conditions or to monitor response to therapies.

**Interpretation:** A beta-amyloid (1-42; Abeta42) result greater than 1026 pg/mL is consistent with a negative amyloid positron emission tomography (PET) scan. A negative amyloid PET scan indicates the presence of no or sparse neuritic plaques and is inconsistent with a neuropathological diagnosis of Alzheimer disease (AD). An Abeta42 result greater than 1026 pg/mL is associated with a reduced likelihood that a patient's cognitive impairment is due to AD. Total Tau (t-Tau) and phosphorylated Tau (p-Tau181) cerebrospinal fluid (CSF) concentrations increase approximately 2 to 3-times as much in patients with mild-moderate AD as compared to age-matched controls. A t-Tau and/or p-Tau181 concentration of less than or equal to 238 pg/mL and less than or equal to 21.7 pg/mL, respectively, reduces the likelihood that a patient's cognitive impairment is due to AD. The use of p-Tau181/Abeta42 ratio provides better concordance with amyloid PET scan when compared to Abeta42, p-Tau181 and t-Tau individually. A cut-off of 0.023 provides optimal balance between NPA (negative % agreement) and PPA (positive % agreement) when compared to amyloid PET results. A p-Tau181/Abeta42 ratio of less than or equal to 0.023 has a 92% NPA with normal amyloid PET. A ratio of greater than 0.023 has a 92% PPA with abnormal amyloid PET. High CSF t-Tau protein concentrations are found in other neurodegenerative diseases such as prion disease or Creutzfeldt-Jakob disease (CJD). In this situation, an elevated t-Tau concentration and an increased t-Tau to p-Tau ratio has a very high specificity for differential diagnoses of CJD. Abnormal (+)/Normal (-) Individual comments for AD reporting values Abeta42 (-) phospho Tau (-) total Tau (-) Normal concentrations of Abeta42, phospho-Tau, and total-Tau concentrations are present in CSF. These results are not consistent with the presence of
pathological changes associated with Alzheimer's disease. Abeta42 (+) phosho-Tau (-) total-Tau (-)
Abnormal Abeta42 concentrations are present in CSF. Phospho-Tau and total-Tau concentrations are
normal. These results may be consistent with Alzheimer's related pathologic change. Abeta42 (+)
phospho-Tau (+) total-Tau (-) Abnormal Abeta42 and phospho-Tau concentrations are present in CSF.
The total-Tau concentration is normal. These results are consistent with the presence of Alzheimer's
disease. Abeta42 (+) phospho Tau (+) total Tau (+) Abnormal Abeta42, phospho-Tau and total-Tau
centations are present in CSF. These results are consistent with the presence of Alzheimer's disease.

Abeta42 (+) phospho Tau (-) total Tau (+) Abnormal Abeta42, and total-Tau concentrations are
present in CSF. The phospho-Tau concentration is normal. These results may be consistent with Alzheimer's
related pathologic change. Abeta42 (-) phospho-Tau (+) total-Tau (-) Abnormal phospho-Tau
concentrations are present in CSF. Abeta42 and total-Tau concentrations are normal. These results are
not consistent with the presence of pathological changes associated with Alzheimer's disease. Abeta42
(-) phospho tau (-) total Tau (+) Abnormal total-Tau concentrations are present in CSF. The Abeta42
and phospho-Tau concentrations are normal. These results are not consistent with the presence of
pathological changes associated with Alzheimer's disease. Abeta42 (-) phospho-Tau (+) total-Tau (+)
Abnormal phospho-Tau and total-Tau concentrations are present in CSF. The Abeta42 concentration
is normal. These results are not consistent with the presence of pathological changes associated with
Alzheimer's disease. This table and interpretations are based on the National Institute on Aging and
Alzheimer's Association research framework diagnostic recommendations.(1)

Reference Values:
Abeta42: >1026 pg/mL
Total-Tau: < or =238 pg/mL
Phospho-Tau 181: < or =21.7 pg/mL
p-Tau/Abeta42: < or =0.023

Analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in
5. Schindler SE, Gray JD, Gordon BA, et al: Cerebrospinal fluid biomarkers measured by Elecsys assays
compared to amyloid imaging. Alzheimers Dement. 2018 Nov;14(11):1460-1469
routine clinical measurements of amyloid beta and tau. Alzheimers Dement. 2021 Mar 31. doi:
10.1002/alz.12316. Epub ahead of print

FAMAN 91132
Amantadine (Symmetrel)

Reference Values:
Units: ng/mL

Therapeutic range has not been established.

Expected steady state amantadine concentrations in patients receiving recommended daily dosages:
200-1000 ng/mL
Toxicity reported at greater than 2000 ng/mL
Amikacin, Peak, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can been used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

Useful For: Monitoring adequacy of serum concentration during amikacin therapy

Interpretation: For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if the peak serum concentration is maintained >35.0 mcg/mL for a prolonged period of time.

Reference Values:
Peak: 20.0-35.0 mcg/mL Toxic peak: >40.0 mcg/mL


Amikacin, Random, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can been used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

Useful For: Monitoring adequacy of blood concentration during amikacin therapy

Interpretation: For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if, for prolonged periods of time, peak serum concentrations are maintained >35.0 mcg/mL, or trough concentrations are maintained at >10.0 mcg/mL.

Reference Values:
Peak: 20.0-35.0 mcg/mL
Toxic peak: >40.0 mcg/mL
Trough: <8.0 mcg/mL
Toxic trough: >10.0 mcg/mL

TAMIK

Amikacin, Trough, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

Useful For: Monitoring adequate clearance of amikacin near the end of a dosing cycle

Interpretation: For conventional (nonpulse) dosing protocols, trough concentrations should fall to <8.0 mcg/mL. Toxicity may occur if the trough serum concentration is maintained >10.0 mcg/mL for prolonged periods of time.

Reference Values:
Trough: <8.0 mcg/mL
Toxic trough: >10.0 mcg/mL


AAMSD

Amino Acids, Maple Syrup Urine Disease Panel, Plasma

Clinical Information: Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). A MSUD can be divided into 5 phenotypes: classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3)-deficient, depending on the clinical presentation and response to thiamin administration. Classic MSUD, the most common and most severe form, presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor to urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Age of onset for individuals with variant forms of MSUD is variable and some have initial symptoms as early as 2 years of age. Symptoms include poor growth and feeding, irritability, and developmental delays. These patients can also experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress. MSUD is a panethnic condition but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1:760 live births. The incidence of MSUD is approximately 1:185,000 live births in the general population. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and allo-isoleucine concentrations. Orthotopic liver transplantation has been used with success and is an effective therapy for MSUD.

Useful For: Follow-up of patients with maple syrup urine disease Monitoring of dietary compliance for...
patients with maple syrup urine disease

**Interpretation:** The quantitative results of isoleucine, leucine, valine, and allo-isoleucine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

**Reference Values:**

**ISOLEUCINE**
- < or =23 months: 31-105 nmol/mL
- 2-17 years: 30-111 nmol/mL
- > or =18 years: 36-107 nmol/mL

**LEUCINE**
- < or =23 months: 48-175 nmol/mL
- 2-17 years: 51-196 nmol/mL
- > or =18 years: 68-183 nmol/mL

**VALINE**
- < or =23 months: 83-300 nmol/mL
- 2-17 years: 106-320 nmol/mL
- > or =18 years: 136-309 nmol/mL

**ALLO-ISOLEUCINE**
- < or =23 months: <2 nmol/mL
- 2-17 years: <3 nmol/mL
- > or =18 years: <5 nmol/mL

**Clinical References:**

**Amino Acids, Quantitative, Plasma**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism, such as phenylketonuria and tyrosinemia, have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and possibly death. Treatment for amino acid disorders includes very specific dietary modifications. Nonessential amino acids are synthesized by the body, while essential amino acids are not and must be obtained through an individual's diet. Therapeutic diets are coordinated and closely monitored by a dietician and/or physician. They are structured to provide the necessary balance of amino acids with particular attention to essential amino acids and those that accumulate in a particular disorder. Patients must pay close attention to the protein content in their diet and generally need to supplement with medical formulas and foods. Dietary
compliance is monitored by periodic analysis of plasma amino acids. In addition, plasma amino acid analysis may have clinical importance in the evaluation of several acquired conditions including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns.

**Useful For:** Evaluation of patients with possible inborn errors of metabolism using plasma specimens. May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns.

**Interpretation:** When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Plasma Amino Acid Reference Values (nmol/mL)</th>
<th>Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=191)</td>
</tr>
<tr>
<td><strong>Phosphoserine (PSer)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Phosphoethanolamine (PEtN)</strong></td>
<td></td>
</tr>
<tr>
<td>Taurine (Tau)</td>
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<tr>
<td>Asparagine (Asn)</td>
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<td>Serine (Ser)</td>
<td>69-271</td>
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<tr>
<td>Hydroxyproline (Hyp)</td>
<td>8-61</td>
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<td>Glycine (Gly)</td>
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<td>Ethanolamine (EtN)</td>
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<td>Threonine (Thr)</td>
<td>47-237</td>
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<td>Citrulline (Cit)</td>
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<td>Sarcosine (Sar)</td>
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<tr>
<td>b-Alanine (bAla)</td>
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<td>Alanine (Ala)</td>
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<td>1-Methylhistidine (1MHis)</td>
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<td>3-Methylhistidine (3MHis)</td>
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<td>Carnosine (Car)</td>
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<td>Anserine (Ans)</td>
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<td>Homocitruline (Hcit)</td>
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<td>Arginine (Arg)</td>
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<tr>
<td>Amino Acid</td>
<td>Lower Limit</td>
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<tr>
<td>a-Aminoadipic Acid (Aad)</td>
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<tr>
<td>g-Amino-n-butyric Acid (GABA)</td>
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<tr>
<td>b-Aminoisobutyric Acid (bAib)</td>
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<td>a-Amino-n-butyric Acid (Abu)</td>
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<td>Hydroxylysine (Hyl)</td>
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<td>Proline (Pro)</td>
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<td>Ornithine (Orn)</td>
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<td>Cystathionine (Cth)</td>
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<td>Cystine (Cys)</td>
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<td>Lysine (Lys)</td>
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<td>Tyrosine (Tyr)</td>
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<td>Isoleucine (Ile)</td>
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<td>Phenylalanine (Phe)</td>
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**Clinical References:**

**Amino Acids, Quantitative, Random, Urine**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism that affect amino acid transport or metabolism have been identified, such as phenylketonuria and tyrosinemia. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and possibly death. In addition, amino acid analysis may have clinical importance in the evaluation of several acquired conditions including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns. General elevations in urine amino acid levels, called aminoaciduria, can be seen in disorders with amino acid transport defects such as lysinuric protein intolerance and Hartnup disease, as well as in conditions with renal tubular dysfunction including Lowe syndrome and Dent disease.

**Useful For:** Evaluating patients with possible inborn errors of metabolism using random urine specimens may aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns.
**Interpretation:** When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Urine Amino Acid Reference Values Age Groups (nmol/mg creatinine)</th>
<th>&lt; or =12 Months (n=515)</th>
<th>13-35 Months (n=210)</th>
<th>3-6 Years (n=197)</th>
<th>7-8 Years (n=74)</th>
<th>9-17 Years (n=214)</th>
<th>&gt; or =18 Years (n=835)</th>
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</thead>
<tbody>
<tr>
<td>Phosphoserine</td>
<td>PSer</td>
<td>(15-341)</td>
<td>(33-342)</td>
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<td>(57-2235)</td>
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<td>Asn</td>
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<td>(362-18614)</td>
<td>(627-6914)</td>
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<td>Glycine</td>
<td>Gly</td>
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<td>(263-2979)</td>
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<td>(18-1629)</td>
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<td>(16-616)</td>
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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Alpha-amino-n-butyric Acid  Abu
Hydroxylysine  Hyl
Proline  Pro  28-2029
Ornithine  Orn
Cystathionine  Cth
Cystine  Cys  12-504  11-133  10-98
Methionine  Met
Valine  Val  11-211  11-211  16-91  11-61
Tyrosine  Tyr  39-685  38-479  23-254  22-245  12-208  15-115
Isoleucine  Ile
Leucine  Leu  15-167  12-100  13-73
Phenylalanine  Phe  14-280  34-254  20-150  21-106  11-111  13-70
Tryptophan  Trp  14-315  14-315  10-303  10-303  15-229  18-114
Allo-isoleucine  AlloIle


**Amino Acids, Quantitative, Spinal Fluid**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism that affect amino acid transport and metabolism have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and death. Cerebrospinal fluid (CSF) specimens are highly informative for a subset of these conditions, such as nonketotic hyperglycinemia and serine biosynthesis defects. CSF specimens are most informative when a plasma specimen is drawn at the same time and the ratio of the amino acid concentrations in CSF to plasma is calculated.

**Useful For:** Evaluating patients with possible inborn errors of amino acid metabolism, in particular nonketotic hyperglycinemia (glycine encephalopathy) and serine biosynthesis defects, especially when used in conjunction with concomitantly collected plasma specimens

**Interpretation:** When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is provided. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who
may provide these studies, and the telephone number to reach one of the laboratory directors in case the referring physician has additional questions.

### Reference Values:

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<th>Reference Values Age Groups</th>
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<td>Sarcosine (Sar)</td>
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<td>Gamma-amino-n-butyric Acid (GABA)</td>
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<td>Ornithine (Orn)</td>
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<td>Cystathionine (Cth)</td>
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Cystine (Cys)

Lysine (Lys) 11-63 9-33 10-25 13-42

Methionine (Met)

Valine (Val) 14-61 9-28 8-20 11-40

Tyrosine (Tyr) 8-83 5-24 5-17

Isoleucine (Ile)

Leucine (Leu) 12-41 6-21 7-16 7-29

Phenylalanine (Phe) 7-40 5-18 7-21

Tryptophan (Trp)

Allo-isoleucine (AlloIle)


**AAUCD 60202 Amino Acids, Urea Cycle Disorders Panel, Plasma**

**Clinical Information:** Urea cycle disorders (UCD) are a group of inherited disorders of nitrogen detoxification that result when any of the enzymes in the urea cycle (carbamoylphosphate synthetase I: CPS I; ornithine transcarbamylase: OTC; argininosuccinic acid synthetase; argininosuccinic acid lyase; arginase; or the cofactor producer, N-acetyl glutamate synthetase: NAGS), have deficient or reduced activity. The role of the urea cycle is to metabolize and clear waste nitrogen, and defects in any of the steps of the pathway can result in an accumulation of ammonia, which can be toxic to the nervous system. The urea cycle is also responsible for endogenous production of the amino acids citrulline, ornithine, and arginine. Infants with a complete urea cycle enzyme deficiency typically appear normal at birth, but present with in the neonatal period as ammonia levels rise with lethargy, seizures, hyper- or hypoventilation, and ultimately coma or death. Individuals with partial enzyme deficiency may present later in life, typically following an acute illness or other stressor. Symptoms may be less severe and may present with episodes of psychosis, lethargy, cyclical vomiting, and behavioral abnormalities. Patients with impaired ornithine metabolism due to ornithine aminotransferase (OAT) deficiency may present with childhood onset myopia progressing to vision loss in the 4th to 6th decades of life. Patients may or may not have accompanying hyperammonemia, but display marked elevations in plasma ornithine. All of the UCD are inherited as autosomal recessive disorders, with the exception of OTC deficiency, which is X-linked. UCD may be suspected with elevated ammonia, normal anion gap, and a normal glucose. Plasma amino acids can be used to aid in the diagnosis of UCD and may aid in monitoring treatment effectiveness. Measurement of urinary orotic acid, enzyme activity (CPS I, OTC, or NAGS), and molecular genetic testing can help to distinguish the conditions and allows for diagnostic confirmation. Acute treatment for UCD consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, orthotopic liver transplantation has been used with success in treating some patients.

**Useful For:** Differential diagnosis and follow-up of patients with urea cycle disorders

**Interpretation:** The quantitative results of glutamine, ornithine, citrulline, arginine, and
argininosuccinic acid with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

**Reference Values:**

**GLUTAMINE**

< or =23 months: 316-1020 nmol/mL  
2-17 years: 329-976 nmol/mL  
> or =18 years: 371-957 nmol/mL

**ORNITHINE**

< or =23 months: 20-130 nmol/mL  
2-17 years: 22-97 nmol/mL  
> or =18 years: 38-130 nmol/mL

**CITRULLINE**

< or =23 months: 9-38 nmol/mL  
2-17 years: 11-45 nmol/mL  
> or =18 years: 17-46 nmol/mL

**ARGININE**

< or =23 months: 29-134 nmol/mL  
2-17 years: 31-132 nmol/mL  
> or =18 years: 32-120 nmol/mL

**ARGINOSUCCINIC ACID**

<2 nmol/mL  
Reference value applies to all ages.

**Clinical References:**

Aminolevulinic Acid Dehydratase, Washed Erythrocytes

**Clinical Information:** Porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen (PBG) remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 7 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Confirmation of a diagnosis of aminolevulinic acid dehydratase deficiency porphyria using washed erythrocyte specimens. This test is not useful for detecting lead intoxication.

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:** Reference ranges have not been established for patients who are <16 years of age.

- > or =4.0 nmol/L/sec
- 3.5-3.9 nmol/L/sec (indeterminate)
- <3.5 nmol/L/sec (diminished)

5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen (PBG) remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 7 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Preferred confirmation test for the diagnosis of aminolevulinic acid dehydratase deficiency porphyria This test is not useful for detecting lead intoxication.

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:**
Reference ranges have not been established for patients who are <16 years of age.

- > or = 4.0 nmol/L/sec
- 3.5-3.9 nmol/L/sec (indeterminate)
- <3.5 nmol/L/sec (diminished)


**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. See The Heme Biosynthetic Pathway in Special Instruction for more information. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrrias: aminolevulinic acid dehydratase deficiency porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. The excretion of aminolevulinic acid (ALA) can be increased due to one of the inherited acute porphyrias or due to secondary inhibition of ALA dehydratase. Among the secondary causes, acute lead intoxication results in the greatest increases of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication, tyrosinemia type I, alcoholism, and pregnancy. The following algorithms are available in Special Instructions or call 800-533-1710 to discuss testing strategies: -Porphyria (Acute) Testing Algorithm -Porphyria (Cutaneous) Testing Algorithm
**Useful For:** Assistance in the differential diagnosis of the acute hepatic porphyrias

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
- <1 year: < or =10 nmol/mL
- 1-17 years: < or =20 nmol/mL
- > or =18 years: < or =15 nmol/mL

**Clinical References:**

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**Amiodarone, Serum**

**Clinical Information:** Amiodarone is an antiarrhythmic agent used to treat life-threatening arrhythmias; it is typically categorized as a Class III drug (antiarrhythmic agents that are potassium channel blockers) but shows several mechanisms of action. The US Food and Drug Administration approved the use of amiodarone for recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia only after demonstrating lack of response to other antiarrhythmics, but more recent studies have shown amiodarone to be the antiarrhythmic agent of choice for many situations, including atrial fibrillation.(1) Amiodarone can be administered orally or intravenously for cardiac rhythm control. It is 95% protein bound in blood, with a volume of distribution of 60 L/kg. Amiodarone elimination is quite prolonged, with a mean half-life of 53 days. CYP3A4 converts amiodarone to its equally active metabolite, N-desethylamiodarone (DEA), which displays very similar pharmacokinetics and serum concentrations compared with the parent drug.(2) Current therapeutic ranges are based solely on amiodarone, but most individuals will have roughly equivalent concentrations of DEA at steady state.(3) Numerous side effects have been associated with amiodarone. The most common adverse effect is disruption of thyroid function (hypo- or hyperthyroidism) due to amiodarone's structural similarity to thyroid hormones. Neurological and gastrointestinal toxicities are concentration-dependent, whereas thyroid dysfunction, pulmonary fibrosis, and hepatotoxicity are more loosely linked to drug concentration. There is significant potential for drug interactions involving amiodarone, including several other cardioactive drugs (eg, digoxin, verapamil, class I antiarrhythmics [sodium channel blockers]), warfarin, statins, and CYP3A4 substrates.

**Useful For:** Monitoring amiodarone therapy, especially when amiodarone is coadministered with other drugs that may interact Evaluation of possible amiodarone toxicity Assessment of patient compliance

**Interpretation:** Clinical effects generally require serum concentrations above 0.5 mcg/mL. Increased risk of toxicity is associated with amiodarone concentrations above 2.5 mcg/mL. Although therapeutic and toxic ranges are based only on the parent drug, the active metabolite N-desethylamiodarone should be present in similar concentrations to amiodarone.

**Reference Values:**
**AMIODARONE**
**Trough Value**
- 0.5-2.0 mcg/mL: Therapeutic concentration
>2.5 mcg/mL: Toxic concentration

**DESETHYLAMIODARONE:**

No therapeutic range established for desethylamiodarone; activity and serum concentration are similar to parent drug.


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**AMTRP 63506**

**Amitriptyline and Nortriptyline, Serum**

**Clinical Information:** Amitriptyline is a tricyclic antidepressant that is metabolized to nortriptyline, which has similar pharmacologic activity. The relative blood levels of amitriptyline and nortriptyline are highly variable among patients. Amitriptyline is the drug of choice in treatment of depression when the side effect of mild sedation is desirable. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect; blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Amitriptyline displays major cardiac toxicity when the combined serum level of amitriptyline and nortriptyline is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

**Useful For:** Monitoring amitriptyline and nortriptyline serum concentrations during therapy Evaluating potential amitriptyline and nortriptyline toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to amitriptyline when combined serum levels of amitriptyline and nortriptyline are between 80 and 200 ng/mL. Risk of toxicity is increased with combined levels are above 500 ng/mL. Most individuals display optimal response to nortriptyline with serum levels between 70 and 170 ng/mL. Risk of toxicity is increased with nortriptyline levels above 500 ng/mL. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range, thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

**Reference Values:**

**AMITRIPTYLINE AND NORTRIPTYLINE**

Total therapeutic concentration: 80-200 ng/mL

**NORTRIPTYLINE ONLY**

Therapeutic concentration: 70-170 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Ammonia, Plasma

Clinical Information: Ammonia is a waste product of protein catabolism; it is potentially toxic to the central nervous system. Increased plasma ammonia may be indicative of hepatic encephalopathy, hepatic coma in terminal stages of liver cirrhosis, hepatic failure, acute and subacute liver necrosis, and Reye's syndrome. Hyperammonemia may also be found with increasing dietary protein intake. The major cause of hyperammonemia in infants includes inherited deficiencies of urea cycle enzymes, inherited metabolic disorders of organic acids and the dibasic amino acids lysine and ornithine, and severe liver disease.

Useful For: Assisting in the diagnosis of hepatic coma Investigating and monitoring treatment for inborn errors of metabolism Evaluating patients with advanced liver disease

Interpretation: Plasma ammonia concentrations do not correlate well with the degree of hepatic encephalopathy. Elevated ammonia concentration may also be found with increased dietary protein intake. Plasma ammonia concentrations in newborns younger than one week are elevated compared to adults. Values less than or equal to 82 mcmol/L have been observed.

Reference Values: < or =30 mcmol/L


Ammonium, 24 Hour, Urine

Clinical Information: The kidney regulates acid excretion and systemic acid base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus, measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients. The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggest ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggest renal tubular acidosis. Such patients are at risk of calcium phosphate stones. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, citrate is metabolized to bicarbonate (a base), which can increase the urine pH. If the urine pH gets too high, the risk of calcium phosphate stones may have unintentionally been increased. Monitoring the urine ammonium concentration is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient.

Useful For: Diagnosis of the cause of acidosis Diagnosis and treatment of kidney stones

Interpretation: If a patient has acidosis and the amount of ammonium in the urine is low, this is suggestive of a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

Reference Values: 15-56 mmol/24 hour
Reference values have not been established for patients <18 years and >77 years of age. Reference values apply to 24 hour collections.


**RAMCN 36885**

Ammonium, Random, Urine

**Reference Values:**

Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile, Pediatric, Random, Urine.

**RAMBO 606709**

Ammonium, Random, Urine

**Clinical Information:** The kidney regulates acid excretion and systemic acid base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus, measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients. The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggests renal tubular acidosi. Such patients are at risk of calcium phosphate stones. -Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, citrate is metabolized to bicarbonate (a base), which can increase the urine pH. If the urine pH gets too high, the risk of calcium phosphate stones may have unintentionally been increased. Monitoring the urine ammonium concentration is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. (4)

**Useful For:** Diagnosis of the cause of acidosis using random urine specimens Diagnosis and treatment of kidney stones

**Interpretation:** If a patient has acidosis and the amount of ammonium in the urine is low, this is suggestive of a renal tubular acidosi. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

**Reference Values:**

Random: 3-65 mmol/L

No reference values established for <18 years and >77 years of age.

Amobarbital, Serum

**Clinical Information:** Amobarbital is an intermediate-acting barbiturate with hypnotic properties used in short-term treatment of insomnia and to reduce anxiety and provide sedation preoperatively. Amobarbital is administered by intravenous infusion or intramuscular injection. The duration of its hypnotic effect is about 6 to 8 hours. The drug distributes throughout the body, with a volume of distribution of 0.9 to 1.4 L/kg, and about 59% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. Its half-life is about 15 to 40 hours (mean: 25 hours). Excretion occurs mainly in the urine.

**Useful For:** Monitoring amobarbital therapy

**Interpretation:** Amobarbital concentrations above 10 mcg/mL have been associated with toxicity.

**Reference Values:**
- Therapeutic concentration: 1.0-5.0 mcg/mL
- Toxic concentration: >10.0 mcg/mL

**Clinical References:**

Amoxapine (Asendin) and 8-Hydroxyamoxapine

**Reference Values:**
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</table>

Amoxicillin, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to amoxicillin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00-0.34</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FAMP 91171**

**Amphetamine, Serum or Plasma**

**Reference Values:**

Reference Range: 10 – 100 ng/mL

**AMPMX 62712**

**Amphetamine-Type Stimulants Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamines). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine (MDMA, Ecstasy); 3,4-methylenedioxyamphetamine (MDA); and 3,4-methylenedioxyethylamphetamine (MDEA). Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease to synthesize. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDMA and MDEA are metabolized to MDA. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves to the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis. Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters such as low-birth weight. Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

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

**Interpretation:** The presence of any 1 of the following: amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or 3,4-methylenedioxymethamphetamine at >50 ng/g is indicative of in utero exposure up to 5 months before birth.

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations:**
- Amphetamine by LC-MS/MS: 50 ng/g
- Methamphetamine by LC-MS/MS: 50 ng/g
- 3,4-Methylenedioxymethamphetamine by LC-MS/MS: 50 ng/g
- 3,4-Methylenedioxymethamphetamine by LC-MS/MS: 50 ng/g
- 3,4-Methylenedioxymethamphetamine by LC-MS/MS: 50 ng/g

**Clinical References:**


**Amphetamine-Type Stimulants Confirmation, Meconium**

**Clinical Information:** Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamines). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy); 3,4-methylenedioxymethamphetamine (MDA); and 3,4-methylenedioxymethamphetamine (MDEA).(1) Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease to synthesize. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDMA and MDEA are metabolized to MDA.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters such as low-birth weight.(4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns.(5)

**Useful For:** Detection of in utero exposure to amphetamine-type stimulants up to 5 months before birth

**Interpretation:** The presence of any 1 of the following: amphetamine; methamphetamine;
3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or
3,4-methylenedioxyethylamphetamine at greater than 50 ng/g is indicative of in utero exposure up to 5
months before birth.

Reference Values:
Negative
Positives are reported with a quantitative liquid chromatography-tandem mass spectrometry
(LC-MS/MS) result.
LC-MS/MS cutoff concentrations:
Amphetamine: 50 ng/g
Methamphetamine: 50 ng/g
3,4-Methylenedioxyamphetamine: 50 ng/g
3,4-Methylenedioxymethamphetamine: 50 ng/g
3,4-Methylenedioxyethylamphetamine: 50 ng/g

Clinical References:

FASCC 75109
Amphetamines Analysis, Serum

Reference Values:
Reference Range:
Amphetamines: Cutoff: 50

Confirmation Threshold: 10 mg/mL

AMPHX 62711
Amphetamines Confirmation, Chain of Custody, Random, Urine

Clinical Information: Amphetamines are sympathomimetic amines that stimulate central nervous system activity and, in part, suppress appetite. Phenetermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All of the other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of narcolepsy, attention-deficit disorder/attention-deficit hyperactivity disorder, and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. Chain-of-custody is a record of the disposition of a specimen to document the individuals that collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phenetermine,Â methylenedioxymethamphetamine (MDMA), methylenedioxyethylamphetamine (MDEA), and methylenedioxymethamphetamine (MDA: a metabolite of MDMA and MDEA) Providing chain-of-custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of amphetamines in urine at concentrations greater than 500 ng/mL is a
strong indicator that the patient has used these drugs within the past 3 days. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegiline (metabolized to methamphetamine and amphetamine); and clobenzorex, famprofazone, fenethylline, fenproporex, and mfenorex, which are amphetamine pro-drugs.

Reference Values:
Negative

Cutoff concentrations:

- **IMMUNOASSAY SCREEN**
  - <500 ng/mL

- **AMPHEMATINE BY LC-MS/MS**
  - <25 ng/mL

- **METHAMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **PHENTERMINE BY LC-MS/MS**
  - <25 ng/mL

- **METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **PSEUDOEPHEDRINE/EPHEDRINE BY LC-MS/MS**
  - <25 ng/mL reported as negative


**AMPHU**

**Amphetamines Confirmation, Random, Urine**

**Clinical Information:** Amphetamines are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Phentermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All of the other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of narcolepsy, attention-deficit disorder/attention-deficit hyperactivity disorder and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

**Useful For:** Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phentermine, methylenedioxyamphetamine (MDA), methylenedioxyxymethamphetamine (MDMA), and methylenediaxyethy lamphetamine (MDEA)

**Interpretation:** The presence of amphetamines in urine at concentrations greater than 500 ng/mL is a strong indicator that the patient has used one of these drugs within the past 3 days. Methamphetamine has a half-life of 9 to 24 hours and is metabolized by hepatic demethylation to amphetamine. Consequently, a sample containing methamphetamine usually also contains amphetamine.
Amphetamine has a half-life of 4 to 24 hours. Amphetamine is not metabolized to methamphetamine; absence of methamphetamine in the presence of amphetamine indicates the primary drug of abuse is amphetamine. 3,4-Methylenedioxymethamphetamine (Ecstasy, MDMA) is metabolized to 3,4-methylenedioxyamphetamine (MDA). The detection interval in urine for amphetamine type stimulants is typically 3 to 5 days after last ingestion. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegeline, and famprofazone (metabolized to methamphetamine and amphetamine); and clobenzorex, fenproporex, and mefenorex, which are metabolized to amphetamine.

**Reference Values:**

Negative

Cutoff concentrations:

- AMPHETAMINE BY LC-MS/MS <25 ng/mL
- METHAMPHETAMINE BY LC-MS/MS <25 ng/mL
- PHENTERMINE BY LC-MS/MS <25 ng/mL
- METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS <25 ng/mL
- METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS <25 ng/mL
- PSEUDOEPHEDRINE/EPHEDRINE BY LC-MS/MS <25 ng/mL, reported as negative


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**Ampicillin, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to ampicillin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

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**Amylase, Body Fluid**

**Clinical Information:** Pleural fluid: Amylase-rich pleural effusions are commonly associated with pancreatitis, esophageal rupture, malignancy, pneumonia, and liver cirrhosis.(1) Pleural fluid amylase measurement is not routinely indicated though may help to narrow the differential due to these causes. Results should be interpreted in conjunction with serum measurement usually as a ratio of pleural fluid to serum amylase. The ratio of pleural fluid to serum amylase in effusions caused by pancreatic disease is much higher (mean + or - SD = 18 + or - 6.3) versus non-pancreatic disease (4.8 + or - 1.3) (P = 0.003).(2) Isoform analysis revealed that pancreatic amylase is diagnostic of pancreatitis-related pleural effusions, whereas salivary amylase isoforms are more often associated with esophageal rupture and malignancy.(3) Peritoneal fluid: The digestive enzymes amylase and lipase can be measured in the identification of pancreatic fluid in the peritoneal cavity. Concentrations are expected to be elevated and at least several-fold times higher in fluid of pancreatic origin compared to simultaneous concentrations in serum.(4) In contrast, amylase concentration in ascites of non-pancreatic origin was approximately half the plasma value.(5) Drain fluid: Amylase might be measured in a drain fluid to aid in the identification of internal pancreatic fistulas due to chronic pancreatitis or formation of a fistula after surgery.(6,7) Comparison to serum concentrations is recommended with elevations several-fold higher than blood being suggestive of the presence of pancreatic fluid in the drained cavity.

**Useful For:** Evaluation of patients with a pathological accumulation of fluid to determine whether pancreatic inflammation, pancreatic fistula, or esophageal rupture may be contributing Aiding in the diagnosis of pancreatitis

**Interpretation:** Peritoneal and drain fluid amylase activity in non-pancreatic peritoneal fluid is often less than or equal to the serum amylase activity. Ascites associated with pancreatitis typically has amylase activity at least 5-fold greater than serum.(1) Normal pleural fluid amylase activity is typically less than the upper limit of normal serum amylase and has a ratio of pleural fluid amylase to serum amylase ratio less than 1.0.(3) All Other Fluids: Body fluid amylase activity may become elevated due to the presence of pancreatitis, esophageal rupture, or amylase producing neoplasms. Results should be interpreted in conjunction with serum amylase and other clinical findings.

**Reference Values:** An interpretive report will be provided

**Clinical References:** 1. Burgess LJ: Biochemical analysis of pleural, peritoneal and pericardial

FAMYS 57288

**Amylase, Isoenzymes**

**Reference Values:**

**Pancreatic amylase**
- 6-35 months: 2-28 U/L
- 3-6 years: 8-34 U/L
- 7-17 years: 9-39 U/L
- 18 years and older: 12-52 U/L

**Salivary amylase**
- 18 months and older: 9-86 U/L

**Total amylase**
- 3-90 days: 0-30 U/L
- 3-6 months: 7-40 U/L
- 7-8 months: 7-57 U/L
- 9-11 months: 11-70 U/L
- 12-17 months: 11-79 U/L
- 18-35 months: 19-92 U/L
- 3-4 years: 26-106 U/L
- 5-12 years: 30-119 U/L
- 13 years and older: 30-110 U/L

AMLPC 60078

**Amylase, Pancreatic Cyst Fluid**

**Clinical Information:** Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Measurement of amylase in pancreatic cyst fluid is often used in conjunction with tumor markers, carcinoembryonic antigen and CA19-9, as an aid in the differential diagnosis of pancreatic cysts lesions. Amylase seems to be particularly helpful in excluding pancreatic pseudocysts. A number of studies have demonstrated that amylase levels are typically very high, usually in the thousands in pseudocysts, therefore, low amylase values virtually excludes pseudocysts. Based on the evidence available, the American College of Gastroenterology (ACG) practice guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts suggest that an amylase cutoff value of 250 U/L is useful to exclude pseudocysts.

**Useful For:** Aiding in distinguishing between pseudocysts and other types of pancreatic cysts, when used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers

**Interpretation:** A pancreatic cyst fluid amylase concentration of less than 250 U/L indicates a low risk of a pseudocyst and is more consistent with cystic neoplasms such as mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasm (IPMN), serous cystadenomas, cystic neuroendocrine tumor, and mucinous cystadenocarcinoma. High pancreatic cyst fluid amylase values are nonspecific and occur both
in pseudocysts and some mucin-producing cystic neoplasms including MCN, IPMN, and mucinous
cystadenocarcinoma. In-house studies to verify this cutoff value showed that 94% (66/70) of pseudocysts
had a value of greater or equal to 250 U/L. Cysts with amylase levels of less than 250 U/L included 69%
of adenocarcinomas, 31% of intraductal papillary mucinous neoplasia, 55% of mucinous cystadenomas,
64% serous cystadenomas, and 6% of pseudocysts. Therefore, using a cutoff of less than 250 U/L to
exclude a pseudocyst has 94% sensitivity and 42% specificity.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Snozek CL, Mascarenhas RC, O'Kane DJ: Use of cyst fluid CEA,
Waaij LA, van Dullemen HM, Porte RJ: Cyst fluid analysis in the differential diagnosis of pancreatic
ACG clinical guideline for the diagnosis and management of pancreatic cysts. Am J Gastroenterol.

PAMY 606893

Amylase, Pancreatic, Serum

Clinical Information: Amylases degrade complex carbohydrates (starches) into simple sugars.
Two isoenzymes, pancreatic and salivary, are found in serum. Serum pancreatic amylase should always
be interpreted in a context of total amylase to determine the relative contribution of salivary and
pancreatic isoenzymes. Imaging tests have become the diagnostic tests of choice for diagnosing
pancreatitis. Pancreatic isoamylase may be used as an adjunct to totally serum amylase, serum lipase,
and imaging tests.

Useful For: Aiding in the evaluation of acute pancreatitis This test is not useful for diagnosing or
characterizing pancreatic cancer or cysts.

Interpretation: Increased concentrations of pancreatic amylase isoenzymes in a context of elevated
total serum amylase may indicate pancreatitis.

Reference Values:
0-<24 months: 0-20 U/L
2-<18 years: 9-35 U/L
> or =18 years: 13-53 U/L

Clinical References: Panteghini M: Laboratory evaluation of pancreatic diseases. Biochimica
Clinica. 2010;34(1):19-25

AMS 8352

Amylase, Total, Serum

Clinical Information: The amylase enzymes are a group of hydrolases that degrade complex
carbohydrates into fragments. Amylase is produced primarily by the exocrine pancreas where the
enzyme is synthesized by the acinar cells and then secreted into the intestinal tract by way of the
pancreatic duct system. Amylases also are produced by the salivary glands, small intestine mucosa,
ovaries, placenta, liver, and fallopian tubes. Pancreatic and salivary isoenzymes are found in serum.

Useful For: Diagnosis and management of pancreatitis Evaluation of pancreatic function

Interpretation: In acute pancreatitis, a transient rise in serum amylase activity occurs within 2 to 12
hours of onset; levels return to normal by the third or fourth day. A 4- to 6-fold elevation of amylase
activity above the reference limit is usual with the maximal levels obtained in 12 to 72 hours. However,
a significant number of subjects show lesser elevations and sometimes none. The magnitude of the
elevation of serum enzyme activity is not related to the severity of pancreatic involvement.
Normalization is not necessarily a sign of resolution. In acute pancreatitis associated with
hyperlipidemia, serum amylase activity may be spuriously normal; the amylasemia may be unmasked.
either by serial dilution of the serum or ultracentrifugation. A significant amount of serum amylase is excreted in the urine and, therefore, elevation of serum activity is reflected in the rise of urinary amylase activity. Urine amylase, as compared to serum amylase, appears to be more frequently elevated, reaches higher levels, and persists for longer periods. However, the receiver operator curves (ROC) of various serum and urine amylase assays demonstrated that all urine assays had poorer diagnostic utility than all serum assays. In quiescent chronic pancreatitis, both serum and urine activities are usually subnormal. Because it is produced by several organs, amylase is not a specific indicator of pancreatic function. Elevated levels also may be seen in a number of nonpancreatic disease processes including mumps, salivary duct obstruction, ectopic pregnancy, and intestinal obstruction/infarction.

**Reference Values:**

0-30 days: 0-6 U/L  
31-182 days: 1-17 U/L  
183-365 days: 6-44 U/L  
1-3 years: 8-79 U/L  
4-17 years: 21-110 U/L  
> or =18 years: 28-100 U/L


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**Amyloid A (Hepatic) Immunostain, Technical Component Only**

**Clinical Information:** Amyloid A (AA), also called serum amyloid A (SAA), is an acute-phase protein. In the liver, AA is expressed on hepatocytes, although expression has been observed in adipocytes. AA can be used with a panel of immunohistochemical markers (beta-catenin, liver fatty acid binding protein, C-reactive protein, and glutamine synthetase) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. AA, along with C-reactive protein is overexpressed in inflammatory (type 3) hepatic adenoma and is not detectable in normal liver or in other adenoma types.

**Useful For:** Classification of hepatic adenomas

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**Amyloid A (SAA) Immunostain, Technical Component Only**

**Clinical Information:** Immunohistochemical staining for amyloid A (SAA) produces diffuse, extracellular staining in positive tissues and colocalizes with Congo Red apple-green birefringence. SAA-type amyloid is associated with chronic inflammatory conditions, such as tuberculosis and rheumatoid arthritis. Immunohistochemical classification of amyloid has been largely replaced by subtyping using tandem mass spectrometry analysis on formalin-fixed paraffin-embedded specimens, due to its superior sensitivity and specificity.
Useful For: Identification and classification of amyloid subtypes in tissue

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

FABP
91408

Amyloid Beta-Protein

Clinical Information: Amyloid B-Protein is a peptide that ranges in size from 28-43 amino acids. Most fragments have the same biological activity as the whole molecule. Amyloid B-Protein causes vascular and cerebral plaque formation. Insoluble fibrils of Amyloid B-Protein accumulate in adrenal blood vessels and in neuritic plaques. Occurrence of plaques are present in normal brain but in a much less dense degree as in Alzheimer's disease patients. Amyloid B-Protein is also found in elevated levels in patients with Down's Syndrome. Substance P has been found to counteract the effects of Amyloid B-Protein.

Reference Values:
Adult Reference Range(s):
20-80 pg/ml

AMYPI
70549

Amyloid P (SAP) Immunostain, Technical Component Only

Clinical Information: Amyloid P (SAP) is a serum protein that is generally incorporated into the extracellular deposits of all amyloid types. Immunohistochemical staining for SAF produces diffuse, extracellular staining in positive tissues, and colocalizes with Congo Red apple-green birefringence. All types of amyloid should be positive for SAP. Immunohistochemical classification of amyloid has been largely replaced by subtyping using tandem mass spectrometry analysis on formalin-fixed paraffin-embedded specimens, due to its superior sensitivity and specificity.

Useful For: Identification of amyloid deposits in tissue

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a
qualified pathologist.


**APPI 70357**

**Amyloid Precursor Protein (APP) Immunostain, Technical Component Only**

**Clinical Information:** Amyloid precursor protein (APP) is present in Alzheimer disease-associated plaques, large pyramidal cells as well as smaller neurons, astrocytes, and microglia. Histologic features of Alzheimer disease include the presence of abundant neurofibrillary, tangles, neuropil threads, and neuritic (“senile”) plaques. The main component of senile plaque amyloid is a 39- to 42-amino acid segment referred to as beta amyloid, which is derived from APP.

**Useful For:** Aids in the identification of amyloid precursor protein present in Alzheimer disease

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**AMPIP 70356**

**Amyloid Protein Identification, Paraffin, LC-MS/MS**

**Clinical Information:** Amyloidosis is a group of hereditary and acquired diseases that are unified by extracellular tissue deposition of misfolded proteins resulting in end organ damage. Amyloidosis can be a systemic or localized disease. Although many cases of amyloidosis are hereditary, most are acquired as the result of an underlying monoclonal B-cell/plasma cell malignancy, as a phenomenon of aging, or as the result of long-standing chronic inflammation. Specific amyloid-related diseases are therefore associated with specific amyloid proteins. These include kappa or lambda immunoglobulin light chains (AL amyloid), transthyretin (ATTR amyloid), serum amyloid A (SAA amyloid), and other uncommon subtypes. Because treatment of amyloidosis patients differs radically for the different amyloid subtypes, it is critically important to accurately identify the proteins that constitute the amyloid deposits. The basic diagnosis of amyloidosis is typically achieved by Congo red staining of paraffin-embedded tissue biopsy specimens obtained from diverse anatomic sites and demonstrating Congo red-positive, apple-green birefringent, amyloid deposits in the tissues. The next step is to definitively subtype the amyloid deposits. This test fulfills that need. It relies on laser microdissection of Congo red-positive amyloid deposits followed by analysis by liquid chromatography-tandem mass spectrometry to accurately determine the identity of the proteins that constitute the amyloid.

**Useful For:** Definitive identification of amyloid proteins
**Interpretation:** An interpretation will be provided.

**Clinical References:**

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**Amyloidosis, Transthyretin-Associated Familial, Reflex, Blood**

**Clinical Information:** The amyloidoses are a group of diseases that result from the abnormal deposition of amyloid in various tissues of the body. They have been classified into 3 major types: primary, secondary, and hereditary. The most common form of amyloidosis (AL) is a disease of the bone marrow called primary systemic AL (immunoglobulin light chain). Secondary AL usually occurs in tandem with chronic infectious or inflammatory diseases, such as rheumatoid arthritis, tuberculosis, or osteomyelitis. Familial or hereditary AL is the least common form. Determining the specific type of AL is imperative in order to provide both an accurate prognosis and appropriate therapies. Familial or hereditary transthyretin AL is an autosomal dominant disorder caused by mutations in the transthyretin gene (TTR). The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic transthyretin (TTR) protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Affected individuals may present with a variety of symptoms including sensorimotor and autonomic neuropathy, vitreous opacities, cardiomyopathy, nephropathy, and gastrointestinal dysfunction. TTR-associated AL is progressive over a course of 5 to 15 years and usually ends in death from cardiac or renal failure or malnutrition. Orthotopic liver transplantation is a treatment option for some patients who are diagnosed in early stages of the disease. Mayo Clinic Laboratories recommends a testing strategy that includes both protein analysis by mass spectrometry (MS) and TTR gene analysis by DNA sequencing for patients in whom TTR-associated familial AL is suspected. The structure of TTR protein in plasma is first determined by MS. The presence of a pathogenic variant in the TTR gene leads to conformational changes in the TTR protein. This ultimately disrupts the stability of the mature TTR protein tetramer, leading to increased amounts of pro-amyloidogenic TTR monomers in the plasma of affected individuals. MS is able to identify mass difference between wild type TTR and variant TTR protein. Only the transthyretin (also known as prealbumin) is analyzed for amino acid substitutions. Other proteins involved in other less common forms of familial amyloidosis are not examined. If no alterations are detected, gene analysis will not be performed unless requested by the provider (ie, when the diagnosis is still strongly suspected; to rule out the possibility of a false-negative by MS). In all cases demonstrating a structural change by MS, the entire TTR gene will be analyzed by DNA sequence analysis to identify and characterize the observed alteration (gene mutation or benign polymorphism). More than 90 mutations that cause TTR-associated familial AL have now been identified within the TTR gene. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of AL. For predictive testing in cases where a familial mutation is known, testing for the specific mutation by DNA sequence analysis (FMTT / Familial Mutation, Targeted Testing) is recommended. These assays do not detect mutations associated with non-TTR forms of familial AL. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

**Useful For:** Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

**Interpretation:** The presence of a structural change in transthyretin (TTR) is suggestive of a gene mutation that requires confirmation by DNA sequence analysis. A negative result by mass spectrometry does not rule out a TTR mutation. Mass spectrometric (MS) results are falsely negative if the amino
acid substitution does not produce a measurable mass shift for the transthyretin mutation. Approximately 90% of the TTR mutations are positive by MS (see Cautions). After identification of the mutation at the DNA level, predictive testing for at-risk family members can be performed by molecular analysis (FMTT / Familial Mutation, Targeted Testing).

Reference Values:
An interpretive report will be provided.


ANAID 45010  An aerobe Ident (Bill Only)

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

ISAN 45255  An aerobe Identification by Sequencing (Bill Only)

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

BATTA 80931  An aerobe Suscep Battery (Bill Only)

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

SANA 45337  An aerobe Suscep per Agent (Bill Only)

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

ANAP 81157  Anaplasma phagocytophilum (Human Granulocytic Ehrlichiosis) Antibody, Serum

Clinical Information: Anaplasma phagocytophilum, an intracellular rickettsia-like bacterium, preferentially infects granulocytes and forms inclusion bodies, referred to as morulae. A phagocytophilum is transmitted by Ixodes species ticks, which also transmit Borrelia burgdorferi and Babesia species. Infection with A phagocytophilum is also referred to as human granulocytic anaplasmosis (HGA) and
symptoms in otherwise healthy individuals are often mild and nonspecific, including fever, myalgia, arthralgia, and nausea. Clues to the diagnosis of anaplasmosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated liver enzymes. HGA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease.

**Useful For:** As an adjunct in the diagnosis of human granulocytic ehrlichiosis Seroepidemiological surveys of the prevalence of the infection in certain populations

**Interpretation:** A positive result of an immunofluorescence assay (IFA) test (titer $\geq 1:64$) suggests current or previous infection with human granulocytic ehrlichiosis. In general, the higher the titer, the more likely it is that the patient has an active infection. Seroconversion may also be demonstrated by a significant increase in IFA titers. During the acute phase of the infection, serologic tests are often nonreactive, polymerase chain reaction (PCR) testing is available to aid in the diagnosis of these cases (see EHRL / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood).

**Reference Values:**

$<1:64$

Reference values apply to all ages.

**Clinical References:** Center for Disease Control and Prevention (CDC): Tick-borne diseases of the United States: A Reference Manual for Health Care Providers. 5th ed. CDC; 2018

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**ALK 70354**

**Anaplastic Lymphoma Kinase Immunostain, Technical Component Only**

**Clinical Information:** A subset of anaplastic large-cell lymphomas shows overexpression of anaplastic lymphoma kinase (ALK-1) protein, resulting from a translocation involving the ALK1 gene. The abnormal ALK-1 expression can be in a nuclear or cytoplasmic distribution. Overexpression of ALK-1 protein is also useful in the diagnosis of lung adenocarcinoma and inflammatory myofibroblastic tumor. In normal tissue ALK-1 is negative.

**Useful For:** Identification of anaplastic lymphoma kinase overexpression Diagnosis of lung adenocarcinoma and inflammatory myofibroblastic tumor

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**ANPAT 70318**

**Anatomic Pathology Consultation, Wet Tissue**

**Clinical Information:** Mayo Clinic Rochester is staffed by pathologists whose expertise and special interests cover the entirety of Pathology, from surgical pathology with all of its respective subspecialty areas, to Hematopathology, Renal Pathology, and Dermatopathology. Consultation services are provided for difficult diagnostic problems. Consultation cases may be sent by a referring pathologist
and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and sometimes transferred between the pathologists, as deemed appropriate for the type of case or diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Materials received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. The goal is to provide the highest possible level of diagnostic consultative service, while trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

**Useful For:** Obtaining a rapid, expert opinion on unprocessed specimens referred by the pathologist

This test is not useful for suspected hematologic disorders

**Interpretation:** Results of the consultation are reported in a formal pathology report, which includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call. The formal pathology report is faxed.

**Reference Values:**
The laboratory will provide a pathology consultation.

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**ANCH 82345**

**Anchovy, IgE, Serum**

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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### Androgen Receptor Immunostain, Technical Component Only

**Clinical Information:** Androgen receptor binds testosterone and 5 alpha-dihydrotestosterone and mediates the biologic action of these sex hormones. It is normally expressed in a wide variety of tissues, including the epithelium and stromal cells of the prostate, endometrium, ovary, and breast. Cells of meningiomas and the pituitary gland may also be positive.

**Useful For:** Identification of tumors that express androgen receptor

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### Androstanediol Glucuronide (Endocrine Sciences)

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal Children</td>
<td>Not Established</td>
</tr>
<tr>
<td>Adult Males</td>
<td>112-1046 ng/dL</td>
</tr>
</tbody>
</table>
| Adult Females            | 11-249 ng/dL       | Occasionally, normal females with no evidence of hirsutism may have levels well beyond the normal range.

### Androstenedione, Serum

**Clinical Information:** Androstenedione is secreted predominately by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). It is also produced ACTH-independent in the testes and ovaries from adrenal-secreted dehydroepiandrosterone sulfate
Androstenedione is a crucial sex-steroid precursor. It lies at the convergence of the 2 biosynthetic pathways that lead from the progestins to the sex-steroids, being derived either via: -C3-dehydrogenation of dehydroepiandrosterone (DHEA) -Catalyzed by 3-beta-hydroxysteroid dehydrogenase-2 (adrenals and gonads) -17,20-lyase (CYP17A1)-mediated side-chain cleavage of 17-alpha-hydroxyprogesterone (OHPG) Androstenedione production during life mimics the pattern of other androgen precursors. Fetal serum concentrations increase throughout embryonal development and peak near birth at approximately young adult levels. Levels then fall rapidly during the first year of life to low prepubertal values. With the onset of adrenarche, androstenedione rises gradually, a process that accelerates with the onset of puberty, reaching adult levels around age 18. Adrenarche is a poorly understood phenomenon peculiar to higher primates that is characterized by a gradual rise in adrenal androgen production. It precedes puberty, but is not causally linked to it. Early adrenarche is not associated with early puberty, or with any reduction in final height, or overt androgenization, and is generally regarded as a benign condition not requiring intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Elevated androstenedione levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild symptoms of estrogen excess, such as gynecomastia. Most mild-to-moderate elevations in androstenedione are idiopathic. However, pronounced elevations of androstenedione may be indicative of androgen-producing adrenal or gonadal tumors. In children, adrenal and gonadal tumors are uncommon, but many forms of congenital adrenal hyperplasia can increase serum androstenedione concentrations. Diagnosis always requires measurement of other androgen precursors (eg, OHPG, 17-alpha-hydroxyprogrenolone, and DHEA-S) and cortisol, in addition to androstenedione. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex-steroids). An initial workup in adults might also include total and bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) and other androgenic steroids (eg, dehydroepiandrosterone sulfate [DHEA-S]). Diagnosis of congenital adrenal hyperplasia (CAH), in conjunction with measurement of other androgenic precursors, particularly, 17-alpha-hydroxyprogesterone (OHPG) (OHPG / 17-Hydroxyprogesterone, Serum), 17 alpha-hydroxyprogrenolone, DHEA-S (DHEA-S / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), and cortisol (CORT / Cortisol, Serum). Monitoring CAH treatment, in conjunction with testosterone (TTST / Testosterone, Total, Serum), OHPG (OHPG / 17-Hydroxyprogesterone, Serum), DHEA-S (DHEA-S / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), and DHEA (DHEA / Dehydroepiandrosterone [DHEA], Serum). Diagnosis of premature adrenarche, in conjunction with gonadotropins (FSH / Follicle-Stimulating Hormone [FSH], Serum; LH / Luteinizing Hormone [LH], Serum) and other adrenal and gonadal sex-steroids and their precursors (TTBS / Testosterone, Total and Bioavailable, Serum or TGRP / Testosterone, Total and Free, Serum; EEST / Estradiol, Serum; DHES / Dehydroepiandrosterone Sulfate [DHEA-S], Serum; DHEA_ / Dehydroepiandrosterone [DHEA], Serum; SHBG / Sex Hormone Binding Globulin [SHBG], Serum; OHPG / 17-Hydroxyprogesterone, Serum).

**Interpretation:** Elevated androstenedione levels indicate increased adrenal or gonadal androgen production. Mild elevations in adults are usually idiopathic, or related to conditions such as polycystic ovarian syndrome (PCOS) in women, or use of androstenedione supplements in men and women. However, levels greater than or equal to 500 ng/dL can suggest the presence of an androgen-secreting adrenal, or less commonly, a gonadal, tumor. Androstenedione levels are elevated in more than 90% of patients with benign androgen-producing adrenal tumors, usually well above 500 ng/dL. Most androgen-secreting adrenal carcinomas also exhibit elevated androstenedione levels, but more typically show relatively larger elevations in 17-alpha-hydroxyprogesterone (OHPG) and dehydroepiandrosterone sulfate (DHEA-S) than in androstenedione, as they have often lost the ability to produce downstream androgens. Most androgen-secreting gonadal tumors also overproduce androstenedione, but often to lesser degrees than adrenal tumors. They also overproduce testosterone. In men and in women with high baseline androgen levels (eg, PCOS), the respective elevations of androstenedione and testosterone may not be high enough to allow unequivocal diagnosis of androgen-producing gonadal tumors. In these cases, an elevation of the usual ratio of testosterone to androstenedione of 1, to a ratio of >1.5, is a strong indicator of neoplastic androgen production. Diagnosis and differential diagnosis of congenital adrenal
hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) mutations the most common cause of CAH (>90% of cases), usually have very high levels of androstenedione, often 5- to 10-fold elevations. OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extend as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common, 3 beta HSD-2 deficiency is characterized by low cortisol and substantial elevations in DHEA-S and 17-alpha-hydroxypregnenolone, while androstenedione is either low, normal, or, rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare STAR (steroidogenic acute regulatory protein) deficiency, all steroid hormone levels are low and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and their precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used for treatment modifications. Normal pubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable. Girls below the age of 7 to 8 and boys before age 8 to 9 who present with early development of pubic hair or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty, or both. Measurement of DHEA-S, DHEA, and androstenedione, alongside determination of sensitive estradiol, total and bioavailable or free testosterone, sex hormone binding globulin (SHBG), and luteinizing hormone/follicle-stimulating hormone levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, and to a lesser degree, androstenedione, will be above pubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. See Steroid Pathways in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (Years)</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (pubertal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>9.8-14.5</td>
<td>31-65</td>
</tr>
<tr>
<td>Stage III</td>
<td>10.7-15.4</td>
<td>50-100</td>
</tr>
<tr>
<td>Stage IV</td>
<td>11.8-16.2</td>
<td>48-140</td>
</tr>
<tr>
<td>Stage V</td>
<td>12.8-17.3</td>
<td>65-210 Females*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (Years)</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (pubertal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>9.2-13.7</td>
<td>42-100</td>
</tr>
<tr>
<td>Stage III</td>
<td>10.0-14.4</td>
<td>80-190</td>
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<td>Stage IV</td>
<td>10.7-15.6</td>
<td>77-225</td>
</tr>
<tr>
<td>Stage V</td>
<td>11.8-18.6</td>
<td>80-240 Females*</td>
</tr>
</tbody>
</table>


Angiosarcoma, MYC (8q24) Amplification, FISH, Tissue

Clinical Information: Postradiation cutaneous angiosarcoma is a malignancy associated with very poor outcome and is consequently treated aggressively. Conversely, atypical vascular lesions are also associated with radiation therapy but are considered to be benign and do not require aggressive management. Therefore, the differentiation of these neoplasms is of considerable clinical importance. Postradiation cutaneous angiosarcomas are characterized by high-level amplification of MYC, whereas reactive and benign vascular lesions do not show amplification of MYC. Similar diagnostic difficulties arise in the setting of primary cutaneous vascular lesions. A subset of primary cutaneous angiosarcomas also shows high-level MYC amplification, which can be useful in the differentiation from benign primary cutaneous vascular lesions.

Useful For: Identifying MYC amplification to aid in the differentiation of cutaneous angiosarcomas from atypical vascular lesions after radiotherapy An aid in the diagnosis of primary cutaneous angiosarcoma

Interpretation: The MYC locus is reported as amplified when the MYC:D8Z2 ratio of 2.0 or greater and demonstrates 6 or more copies of the MYC locus. A lesion with a MYC:D8Z2 ratio less than 2.0 or showing a ratio of 2.0 or greater with less than 6 copies of MYC is considered to lack amplification of the MYC locus.

Reference Values: An interpretive report will be provided.

distress syndrome, adults with amyloidosis, and histoplasmosis have been associated with increased serum ACE activity.

**Useful For:** Evaluation of patients with suspected sarcoidosis

**Interpretation:** An elevation in the level of serum angiotensin converting enzyme (ACE), along with radiographic evidence of infiltrates or adenopathy and organ biopsies showing noncaseating epithelial granulomas is suggestive of a diagnosis of sarcoidosis. Normal, healthy children and infants are known to have ACE activity levels greater than the adult reference interval.

**Reference Values:**

- > or =18 years: 16-85 U/L
- 0-17 years: ACE activity may be 20-50% higher in healthy children compared to healthy adults (16-85 U/L).

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

**Clinical References:**

3. Personal observations from a Mayo pediatric normal range study using a manual method (Hana)

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**FANGI**

**Angiotensin I, Plasma**

**Clinical Information:** Angiotensin I is a ten amino acid peptide formed by Renin cleavage of Angiotensinogen (Renin Substrate). Angiotensin I has little biological activity except that high levels can stimulate Catecholamine production. It is metabolized to its biologically active byproduct Angiotensin II by Angiotensin Converting Enzyme (ACE). The formation of Angiotensin I is controlled by negative feedback of Angiotensin II and II on Renin release and by Aldosterone concentration. Levels of Angiotensin I are increased in many types of hypertension. Angiotensin I levels are used to determine Renin activity. Angiotensin I is excreted directly into the urine.

**Reference Values:**

Up to 25 pg/mL

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**ANGII**

**Angiotensin II and Angiotensin (1-7), Plasma**

**Clinical Information:** Direct Angiotensin II (Ang II) if preferable since the final pathway of renin activation is the generation of Ang II by the Angiotensin converting enzyme 2 (ACE2) receptor. The angiotensins (Ang): Ang I (Ang 1-10), Ang II (Ang 1-8), Ang III (Ang 2-8), Ang IV (Ang 3-8), Ang 1-9, Ang 1-7, Ang 1-5, and Ang 1-4 are signaling peptides that are activated through feedback regulated peptidase cascades. Currently, Ang II, Ang III, Ang IV, and Ang 1-7 are considered biologically active with both overlapping and differential actions. Angiotensins are involved in the regulation of almost 100 different biological processes. However, their most prominent effects are regulation of vascular tone and aldosterone secretion. The first step in the angiotensin cascade is mediated by renin, which is produced by the renal juxtaglomerular apparatus in response to increased renal sympathetic activity, reduced renal blood pressure, or decreased sodium and chloride concentrations. Renin cleaves the secreted portion (amino acids 34-485) of angiotensin precursor protein angiotensinogen near its N-terminus. The resultant decapeptide, Ang I, is devoid of biological activity but serves as the reservoir/precursor for the bioactive downstream peptides that are generated by angiotensin converting enzyme 1 (ACE). Traditionally, serum or plasma aldosterone and plasma renin activity (PRA) measurements (amount of Ang I generated per hour at 37 degrees C) have been used to assess the renin-angiotensin system (RAS) in order to assist in the diagnosis of primary aldosteronism (low PRA, high aldosterone) and renal vascular disease (high PRA, high aldosterone). More recently, there has
been increasing interest in direct measurement of Ang II, the most bioactive compound that mediates most of the vasoconstriction via Ang II receptors type 1 and 2, and of Ang 1-7, which has opposing effects through competitive binding to the Ang II receptor and via signaling through the separate MAS1 proto-oncogen receptor (MAS1). Ang 1-7 is one of the Ang II degradation products that are generated by the soluble and membrane-bound variants of angiotensin converting enzyme (ACE2). Direct measurement of Ang II, or of the combination Ang II and Ang 1-7, potentially provides a better estimation of the biological effects of RAS activation than PRA. With possible discontinuation of angiotensin-receptor blockers and ACE inhibitors in patients, therapeutic monitoring and further assessments of RAS or renin-angiotensin-aldosterone system (RAAS) may be necessary. In addition, coronaviruses, including highly pathogenic variants such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and SARS-coronavirus 2 (SARS-CoV-2) effect entry into cells by binding to membrane-bound ACE2, mimicking Ang II binding through their spike proteins. This is followed by ligand dependent endocytosis of the virus. The balance of Ang II and Ang 1-7, and of their respective receptors, in the vicinity of virus-exposed cells, regulates the endocytotic process in an incompletely understood fashion. This has generated intense interest in examining whether ACE inhibitors, Ang II receptor blockers, or other novel drugs might be able to reduce viral entry. In addition, Ang II or Ang 1-7 concentrations and the degree of respective ACE and ACE2 activity might predict severity of coronavirus infections.

**Useful For:** Direct measurement of Angiotensin II (Ang II) and Angiotensin (1-7) (Ang 1-7) in plasma Adjunct to plasma renin activity (PRA) and aldosterone measurements for the diagnosis of primary aldosteronism and renal-vascular hypertension. Adjunct, or alternative to, PRA for investigations of potential associations with outcomes of coronavirus infection. Drug studies as to renin-angiotensin system (RAS) manipulations that might be useful in treatment of cardiovascular diseases or corona virus infection. This test is not useful for establishing eligibility for a specific treatment as results must be interpreted in conjunction with the clinical status of the patient.

**Interpretation:** High angiotensin II (Ang II) concentrations in the absence of angiotensin receptor blockers (ARB) therapy are suggestive of angiotensin-driven hypertension. Low Ang II concentrations in conjunction with low plasma renin activity (PRA) and high serum/plasma aldosterone concentration indicate possible primary aldosteronism. Conversely, if aldosterone is low, renal vascular disease should be suspected. Simultaneous angiotensin (1-7) (Ang 1-7) measurement might allow further assessment of the biological consequences of Ang II signaling, with high Ang 1-7 concentrations suggesting that some of the pressor effects are ameliorated via MAS1 protooncogene signaling by Ang 1-7. For experimental and clinical trial studies for cardiovascular disease and prediction of likely coronavirus infection severity, there are, at the moment, no definitive guidelines and results should be interpreted in the context of each study. Test results are to aid the interpretation of clinical status and optimal paths for further investigation, if any. Test results should always be interpreted in conjunction with all other clinical findings as they cannot be interpreted as absolute evidence for the presence or absence of disease. Note: Advice on stimulation or suppression tests is available from Mayo Clinic’s Division of Endocrinology and may be obtained by calling 800-533-1710. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions.

**Reference Values:**

Angiotensin II: <5-40 pg/mL  
Angiotensin (1-7): <10-55 pg/mL


Current as of June 14, 2021 12:13 pm CDT
Anisakis, Parasite, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to the Anisakis parasite Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference value apply to all ages</td>
</tr>
</tbody>
</table>

testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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

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

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<td>50.0-99.9</td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FABAA 75662 Anti-bestrophin Autoantibodies

Reference Values: A final report will be provided.

FACN1 75620 Anti-cN-1A (NT5c1A) IBM

Clinical Information: Anti-cN-1A autoantibodies in idiopathic inflammatory myopathy (IIM) patients appear to be disease-specific for sporadic Inclusion Body Myositis (sIBM) and are rarely detected in other autoimmune conditions. Anti-cN-1A autoantibodies have a moderate sensitivity, but their high specificity for sIBM may be helpful in the diagnosis of this infrequent and difficult-to-diagnose myopathy. This assay can augment and accelerate the suspected diagnosis of sIBM using sera where muscle biopsy is delayed and/or unfeasible.

Reference Values:
Reference Range: <20

Interpretation:
Negative: <20 units
Weak Positive: 20 - 39 units
Moderate Positive: 40 - 80 units
Strong Positive: >80 units

ADNAS 80204 Anti-DNase B Titer, Serum

Clinical Information: A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonuclease (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

Useful For: Demonstration of acute or recent streptococcal infection using anti-DNase B titer

Interpretation: Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test.
Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test, such as this assay, is recommended.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>&lt; or =250 U/mL</td>
</tr>
<tr>
<td>5-17 years</td>
<td>&lt; or =375 U/mL</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>&lt; or =300 U/mL</td>
</tr>
</tbody>
</table>


**FAEAB**

**Anti-Enterocyte Antibodies**

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Negative</td>
</tr>
<tr>
<td>IgA</td>
<td>Negative</td>
</tr>
<tr>
<td>IgM</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**FIGA**

**Anti-IgA**

**Clinical Information:** For the evaluation of patients with recurrent infection for the possibility of IgA deficiency (IgAD). Patients with IgA deficiency may develop antibodies against IgA that make them susceptible to adverse reactions to blood products including intravenous immunoglobulin.

**Reference Values:**

<99 U/mL

Patients with IgG antibodies against IgA may suffer from anaphylactoid reactions when given IVIG that contains small quantities of IgA. In one study (Clinical Immunology 2007; 122:156) five out of eight patients with IgG anti-IgA antibodies developed anaphylactoid reactions when IVIG was administered.


**FANTI**

**Anti-IgE**

**Reference Values:**

Normal

This ELISA measures IgG antibodies specific for IgE. A result of normal indicates that the level of IgG anti-IgE antibodies is similar to that seen in a population of healthy individuals. A result of elevated indicates an increased level of IgG anti-IgE antibodies compared to healthy individuals. These autoantibodies have been implicated as a causative agent in autoimmune chronic urticaria and atopic dermatitis.
Anti-MDA-5 Ab (CADM-140)

**Clinical Information:** Anti-MDA5 antibodies are present in 7-35% of adult DM. Clinical features consist of absent or mild muscle symptoms (CADM), rapidly progressive ILD, specific mucocutaneous features of skin ulcerations and papules, oral ulcerations and arthritis.

**Reference Values:**
- Negative: <20 units
- Weak Positive: 20-39 units
- Moderate Positive: 40-80 units
- Strong Positive: >80 units

Anti-Mi-2 Ab

**Clinical Information:** Anti-Mi-2 antibodies are found in 10-20% of adult dermatomyositis (DM) and <10% of JDM. They are associated with classic DM features: mild to moderate weakness with shawl rash, heliotrope rash, V-sign, Gottron's papules and have good response to therapy, with lower incidence of cancer compared to Mi-2 negative DM.

**Reference Values:**
- Negative

Anti-Nuclear Antibodies by Indirect Fluorescent Antibody (IFA), Cerebrospinal Fluid

**Useful For:** ANA are commonly found in a variety of autoimmune diseases. Antibody frequency increases with age in apparently healthy people. ANA patterns on Hep-2 slides provide only general clues about particles (chromatin, nucleosomes and spliceosomes). ANA patterns (other than centromere pattern) are not reliably correlated with the presence of specific antibodies and must be further evaluated by EIA using individual ENA antigens.

**Reference Values:**
- ANA by IFA, CSF: Negative
- ANA Pattern: No Pattern

Anti-Nuclear Antibodies, Synovial Fluid

**Useful For:** ANA are commonly found in a variety of autoimmune diseases. Antibody frequency increases with age in apparently healthy people. ANA patterns on Hep-2 slides provide only general clues about particles (chromatin, nucleosomes, and spliceosomes). ANA patterns (other than centromere pattern) are not reliably correlated with the presence of specific antibodies and must be further evaluated by EIA using individual ENA antigens.

**Reference Values:**
- ANA Titer: <1:10
- ANA Pattern: No Pattern

Anti-Phosphatidylcholine Ab

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT
Anti-Phosphatidylcholine IgA: <12.0 U/mL
Anti-Phosphatidylcholine IgG: <12.0 U/mL
Anti-Phosphatidylcholine IgM: <12.0 U/mL

Reference Range applies to Antiphosphatidylcholine IgA, IgG & IgM:
Normal: <12.0
Equivocal: 12.0 – 18.0
Elevated: >18.0

FPHET Anti-Phosphatidylethanolamine Panel

Reference Values:
Anti-Phosphatidylethanolamine IgA
<12.0 U/mL

Anti-Phosphatidylethanolamine IgG
<12.0 U/mL

Anti-Phosphatidylethanolamine IgM
<12.0 U/mL

Reference Range applies to Antiphosphatidylethanolamine IgA, IgG, & IgM
Normal: <12.0
Equivocal: 12.0 – 18.0
Elevated: >18.0

FAPMA Anti-PM/Scl-100 Ab

Clinical Information: The anti-PM/Scl-100 antibody is associated with younger age, calcinosis and has lower rates of gastrointestinal symptoms, ILD and pulmonary hypertension. There is also evidence of a possibly better survival compared to the presence of either anti-PM/Scl-75 or anti-Scl-70 antibodies.

Reference Values:
Reference Range: <20
Interpretation:
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FARWB Anti-retinal autoantibodies follow up, WB

Reference Values:
A final report will be attached in MayoAccess.

FAS1A Anti-SAE1 Ab, IgG

Clinical Information: Anti-SAE 1 IgG autoantibody can be used to assist in the diagnoses and characterization of a subset of dermatomyositis (DM). It is highly specific for DM (>95%) and is present in 5-8% of the European DM population. Initial disease onset may consist of mild myopathic features with severe skin involvement; however, extensive myalgia and muscle disease with weakness can appear...
as the disease progresses. It is associated with dysphagia and systemic symptoms (i.e. fevers, weight loss, increased inflammatory markers). In one cohort, an association with ILD and cancer had been found.

**Reference Values:**
Reference Range: <20

**Interpretation:**
- Negative: <20 units
- Weak Positive: 20-39 units
- Moderate Positive: 40-80 units
- Strong Positive: >80 units

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**Anti-Synthetase Profile**

**Clinical Information:** This Anti-Synthetase Profile is comprised of Anti-Jo-1 Ab, Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab and Anti-OJ Ab. Anti-synthetase syndrome is an autoimmune disease characterized by interstitial lung disease (ILD), non-erosive arthritis, myositis, Raynaudâ€™s phenomenon, unexplained fever and/or mechanicâ€™s hands.

**Reference Values:**
- Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab: Reference Range: Negative
- Anti-Jo-1 Ab: Reference Range: <20
  - Negative: <20 units
  - Weak Positive: 20-39 units
  - Moderate Positive: 40-80 units
  - Strong Positive: >80 units

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**Anti-Th/To Ab**

**Clinical Information:** The Th/To antibodies are present in 10-19% of patients with limited SSc, in 11% of patients with diffuse cutaneous SSc, and in 3% of patients with primary Raynaud's disease. Anti-Th/To antibody has been shown to be highly specific for patients with SSc.

**Reference Values:**
- Negative

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**Anti-TIF-1gamma Antibody**

**Clinical Information:** Anti-TIF-1(P155) antibodies are present in 15-38% of adult DM and 20-30% in JDM. Highly associated with malignancy which is found in 50-75% of positive adult patients; 89% specificity and 78% sensitivity for diagnosing cancer associated DM; no cancer association in children.

**Reference Values:**
- Reference Range: <20
  - Negative: <20 units
  - Weak Positive: 20-39 units
  - Moderate Positive: 40-80 units
  - Strong Positive: >80 units
Anti-U3 RNP Antibodies (Fibrillarin)

**Clinical Information:** The U3-RNP (Fibrillarin) particle is thought to participate in the first step of preribosomal RNA processing. Anti-U3 RNP antibodies have been shown to be highly specific for patients with SSc. Anti-Fibrillarin (U3 RNP) antibodies are highly specific for diffuse SSc with a sensitivity of 4-10%. They are associated with isolated pulmonary arterial hypertension, myositis, renal and cardiac manifestations of SSc. 15% of IIM, mostly found in scleroderma/myositis overlap. Found in 4-10% of Diffuse SSc, <2% in Limited SSc, associated with isolated PAH, myositis, cardiac and renal involvement. More prevalent in African-Americans.

**Reference Values:**
Negative

Antibody Identification, RBC

**Clinical Information:** After exposure to foreign red blood cells via transfusion or pregnancy, some people form antibodies that are capable of the destruction of transfused red cells or of fetal red cells in utero. It is important to identify the antibody specificity in order to assess the antibody's capability of causing clinical harm and, if necessary, to avoid the antigen on transfused red blood cells. Autoantibodies react against the patient's own red cells as well as the majority of cells tested. Autoantibodies can be clinically benign or can hemolyze the patient's own red blood cells, such as in cold agglutinin disease or autoimmune hemolytic anemia.

**Useful For:** Assessing positive pretransfusion antibody screens, transfusion reactions, hemolytic disease of the newborn, and autoimmune hemolytic anemias. This test is not useful for monitoring the efficacy of Rh-immune globulin administration. This test is not useful for identifying antibodies detected only at 4 degrees C or only after extended room temperature incubation.

**Interpretation:** Specificity of alloantibodies will be stated. The patient's red blood cells will be typed for absence of the corresponding antigens or as an aid to identification in complex cases. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

**Reference Values:**
Negative,
If positive, antibodies will be identified and corresponding special red cell antigen typing on patientâ€™s red blood cells will be performed.Å


Antibody Screen with Reflexed Antibody Identification, RBC

**Clinical Information:** Transfusion and pregnancy are the primary means of sensitization to red cell antigens. In a given population, 2% to 4% of the general population possess irregular red cell alloantibodies. Such antibodies may cause hemolytic disease of the newborn or hemolysis of transfused donor red blood cells.

**Useful For:** Detection of allo- or autoantibodies directed against red blood cell antigens in the settings of pretransfusion testing. Evaluation of transfusion reactions. Evaluation of hemolytic anemia.

**Interpretation:** A positive result (antibody detected) necessitates antibody identification to establish the specificity and clinical significance of the antibody detected. Alloantibodies detected on pregnant Mayo Clinic-Rochester patients will be evaluated for the allo-antibody titer. If antibody reacts strongly, the titre test will be performed. Negative results indicate no antibody was detected.

**Reference Values:**
Negative
If positive, antibody identification will be performed.


### Antibody Titer, Whole Blood and Serum

**Clinical Information:** Some maternal IgG alloantibodies to red blood cell antigens will cross the placenta and cause hemolysis of antigen-positive fetal red cells. The resulting fetal anemia and hyperbilirubinemia can be harmful or even fatal to the newborn.

**Useful For:** Monitoring antibody levels during pregnancy to help assess the risk of hemolytic disease of the newborn. This test is not useful for monitoring the efficacy of Rh-immune globulin administration.

**Interpretation:** The specificity of the maternal alloantibody will be stated. The titer result is the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed. If the antibody problem identified is not relevant in hemolytic disease of the newborn or if titrations are not helpful, the titer will be canceled and will be replaced by ABIDR / Antibody Identification, RBC. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

**Reference Values:**

- Negative,
  - If positive, result will be reported as the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed.


### Antibody to Extractable Nuclear Antigen Evaluation, Serum

**Clinical Information:** SSA, SSB, SM, and RNP are extractable nuclear antigens (ENA) that occur in patients with several different connective tissue diseases. Scl 70 (topoisomerase 1) is a 100-kD nuclear and nucleolar enzyme. Scl 70 antibodies are considered to be specific for scleroderma (systemic sclerosis) and are found in up to 60% of patients with this connective tissue disease. Scl 70 antibodies are more common in patients with extensive cutaneous involvement and interstitial pulmonary fibrosis, and are considered a poor prognostic sign. (1) JO1 is a member of the amino acyl-tRNA synthetase family of enzymes found in all nucleated cells and a marker for the disease polymyositis. For more information, see individual unit codes.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive. Testing is not useful in patients without demonstrable antinuclear antibodies.

**Interpretation:** A positive result is consistent with a connective tissue disease. For more information, see individual unit codes.

**Reference Values:**

- SS-A/Ro ANTIBODIES, IgG
  - < 1.0 U (negative)
  - > or = 1.0 U (positive)
  - Reference values apply to all ages.

- SS-B/La ANTIBODIES, IgG
  - < 1.0 U (negative)
  - > or = 1.0 U (positive)
  - Reference values apply to all ages.
Sm ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

RNP ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Scl 70 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Jo 1 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


FADDS
Antidepressant Drug Screen, Qualitative
Reference Values:
Antidepressant screen includes the analysis for:
Amytriptyline, Clomipramine and Desmethylclomipramine, Cyclobenzaprine, Desipramine, Doxepin and Desmethyldoxepin, Fluoxetine and Norfluoxetine, Imipramine, Maprotiline, Nortriptyline, Paroxetine, Protriptyline, Sertraline and Desmethylsertraline, Trimipramine.

FASQN
Antidepressant Drug Screen, Ur, Quantitative
Reference Values:
Antidepressant screen includes the analysis for: amitriptyline, clomipramine and desmethylclomipramine, cyclobenzaprine, desipramine, doxepin and desmethyldoxepin, fluoxetine and norfluoxetine, imipramine, maprotiline, nortriptyline, paroxetine, protriptyline, sertraline and desmethylsertraline, trimipramine.

MMLYP
Antimicrobial Susceptibility Panel, Yeast, Varies
Clinical Information: Candida species are the fourth leading cause of nosocomial infections and are also frequent causes of community-acquired infections. Antifungal susceptibility testing may aid in the management of patients with invasive infections due to Candida species or patients who appear to be experiencing therapeutic failure. The Clinical Laboratory Standards Institute has approved the use of a broth microdilution method for determining the susceptibility of Candida species.

Useful For: Determining in vitro quantitative antifungal susceptibility (minimum inhibitory concentration) of non-fastidious yeast Testing may be warranted to aid in the management of certain circumstances, such as: -Refractory oropharyngeal infections due to Candida species in patients who appear to be experiencing therapeutic failure with standard agents at standard doses -Invasive infections due to Candida species when the utility of azole antifungal agents is uncertain (eg, when the infection is due to a non-Candida albicans organism)
**Interpretation:** The minimum inhibitory concentration (MIC) is recorded as the lowest concentration of antifungal agent producing complete inhibition of growth. Interpretive breakpoints are available for Candida albicans, Candida glabrata, Candida guilliermondii, Candida krusei, Candida parapsilosis, and Candida tropicalis for limited drugs (see tables below); the clinical relevance of testing any other organism-drug combination remains uncertain. Agent MIC Ranges on Yeast Plate (mcg/mL)

**Candida albicans Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Susceptible Dose Dependent</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin</strong></td>
<td>0.125-256 &lt; or =2 4 - &gt; or =8</td>
<td>Itraconazole 0.015-16 - - - -</td>
</tr>
<tr>
<td>5-Flucytosine 0.06-64 - - - -</td>
<td>Voriconazole 0.008-8 &lt; or =0.12 0.25-0.5 - &gt; or =1</td>
<td></td>
</tr>
<tr>
<td>Caspofungin 0.008-8 &lt; or =0.25 - 0.5 &gt; or =1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole 0.008-8 - - - -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Agent MIC Ranges on Yeast Plate (mcg/mL)**

**Candida glabrata Interpretations (mcg/mL)**

<table>
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<td>Voriconazole 0.008-8 - - - - Caspofungin 0.008-8 &lt; or =0.12 - 0.25 &gt; or =1</td>
<td></td>
</tr>
<tr>
<td>Posaconazole 0.008-8 - - - -</td>
<td></td>
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**Candida guilliermondii Interpretations (mcg/mL)**

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<th>Resistant</th>
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<td>Voriconazole 0.008-8 - - - -</td>
<td></td>
</tr>
<tr>
<td>Caspofungin 0.008-8 &lt; or =0.12 - 0.25 &gt; or =1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole 0.008-8 - - - -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Candida krusei Interpretations (mcg/mL)**

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<td>5-Flucytosine 0.06-64 - - - -</td>
<td>Voriconazole 0.008-8 - - - -</td>
<td></td>
</tr>
<tr>
<td>Caspofungin 0.008-8 &lt; or =0.12 - 0.25 &gt; or =1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole 0.008-8 - - - -</td>
<td></td>
<td></td>
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</table>

**Candida parapsilosis Interpretations (mcg/mL)**

<table>
<thead>
<tr>
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<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin</strong></td>
<td>0.125-256 &lt; or =2 4 - &gt; or =8</td>
<td>Itraconazole 0.015-16 - - - -</td>
</tr>
<tr>
<td>5-Flucytosine 0.06-64 - - - -</td>
<td>Voriconazole 0.008-8 - - - -</td>
<td></td>
</tr>
<tr>
<td>Caspofungin 0.008-8 &lt; or =0.12 - 0.25 &gt; or =1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole 0.008-8 - - - -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Candida tropicalis Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Susceptible Dose Dependent</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin</strong></td>
<td>0.125-256 &lt; or =2 4 - &gt; or =8</td>
<td>Itraconazole 0.015-16 - - - -</td>
</tr>
<tr>
<td>5-Flucytosine 0.06-64 - - - -</td>
<td>Voriconazole 0.008-8 - - - -</td>
<td></td>
</tr>
<tr>
<td>Caspofungin 0.008-8 &lt; or =0.12 - 0.25 &gt; or =1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole 0.008-8 - - - -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please note that Candida krusei is intrinsically resistant to fluconazole regardless of in vitro MIC result.

**Reference Values:**
Results reported in mcg/mL


---

**Antimicrobial Susceptibility, Acid-Fast Bacilli, Rapidly Growing, Varies**

**Clinical Information:** There are more than 100 species of rapidly growing mycobacteria and many are significant human pathogens (eg, Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum). Rapidly growing mycobacteria cause a variety of infections including pulmonary infections, skin and soft tissue infections, and disseminated disease. Antimicrobial susceptibility testing of clinically significantly rapidly growing mycobacteria is important to help guide patient care. Antimicrobials tested in this assay are amikacin, cefoxitin, ciprofloxacin, clarithromycin, clofazimine, doxycycline, imipenem, linezolid, moxifloxacin, tigecycline, tobramycin, and trimethoprim/sulfamethoxazole.

**Useful For:** Determination of susceptibility of rapidly growing mycobacteria to the antimicrobial agents on the test panel
**Interpretation:** Results are reported as the minimum inhibitory concentration in micrograms/mL. Interpretive criteria (susceptible, intermediate, or resistant) are reported according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

**Reference Values:**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Susceptible (mcg/mL)</th>
<th>Intermediate (mcg/mL)</th>
<th>Resistant (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt; or =16</td>
<td>32</td>
<td>&gt; or =64</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>&lt; or =16</td>
<td>32-64</td>
<td>&gt; or =128</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =1</td>
<td>2</td>
<td>&gt; or =4</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =2</td>
<td>4</td>
<td>&gt; or =8</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>No interpretations available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>&lt; or =1</td>
<td>2-4</td>
<td>&gt; or =8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&lt; or =4</td>
<td>8-16</td>
<td>&gt; or =32</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt; or =8</td>
<td>16</td>
<td>&gt; or =32</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =1</td>
<td>2</td>
<td>&gt; or =4</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>No interpretations available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&lt; or =2</td>
<td>4</td>
<td>&gt; or =8</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt; or =2/38</td>
<td>-</td>
<td>&gt; or =4/76</td>
</tr>
</tbody>
</table>

**Reference Values:**

Interpretive criteria for *Mycobacterium avium-intracellulare* complex

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Minimum inhibitory concentration (MIC, mcg/mL) for each interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =8</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt; or =8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Amikacin (IV)</td>
<td>&lt; or =16</td>
</tr>
<tr>
<td>Amikacin (liposomal, inhaled)</td>
<td>&lt; or =64</td>
</tr>
</tbody>
</table>

Interpretative criteria for *Mycobacterium kansasii* and other slowly growing mycobacteria

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mcg/mL) for each interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt; or =16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt; or =8</td>
</tr>
<tr>
<td>Minocycline</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>&lt; or =2/38</td>
</tr>
</tbody>
</table>

**Clinical References:**
collected so as not to confuse clinically significant isolates with normal or contaminating microbiota. Susceptibility testing is indicated for any organism that contributes to an infectious process warranting antimicrobial chemotherapy if its susceptibility cannot be reliably predicted from the organism's identity. The MIC obtained during AST is helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. If clinical breakpoints exist, MICs are accompanied by interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, nonsusceptible, or resistant) when applicable.

**Useful For:** Determining the in vitro susceptibility of aerobic bacteria involved in human infections

**Interpretation:** A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. Refer to the "Reference Values" section for interpretation of various categories.

**Reference Values:**
Results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible:**
A category defined by a breakpoint that implies that isolates with an MIC at or below or a zone diameter at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Susceptible-Dose Dependent:**
A category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the susceptible-dose dependent (SDD) category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of a SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function.

**Intermediate:**
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and/or for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

**Resistant:**
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

**Nonsusceptible:**
A category used for isolates for which only a susceptible breakpoint is designated because of the absence...
or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above or the zone diameters are below the value indicated for the susceptible breakpoint should be reported as nonsusceptible.

Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

Epidemiological Cutoff Value:
The MIC that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type or wild-type, respectively). The epidemiological cutoff value (ECV) defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency.

When an ECV is reported, an interpretive category is not assigned, and the following comment will be included: "This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates (WITH / WITHOUT) acquired resistance; however, correlation with treatment outcome is unknown."

(Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. 30th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2020)

Clinical References:

MMLSA 56031

**Antimicrobial Susceptibility, Anaerobic Bacteria, MIC, Varies**

**Clinical Information:** Anaerobic bacteria are the greatest component of the human body's normal bacterial flora. Anaerobes colonize the skin, oral cavity, and genitourinary and lower gastrointestinal tracts and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are compromised, in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes and by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and they are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians. Bacteroides and Parabacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are generally effective agents although resistance to clindamycin, and occasionally ertapenem, is increasing. The minimum inhibitory concentration (MIC) obtained during antimicrobial susceptibility testing is helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. The MICs are accompanied by interpretive categories (ie, susceptible, intermediate, resistant, or epidemiological cutoff value (ECV) when applicable.

**Useful For:** Determining the in vitro susceptibility on isolates of anaerobic bacteria involved in human infections Directing antimicrobial therapy for anaerobic infections

**Interpretation:** A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. Refer to the Reference Values section for interpretation of various antimicrobial categories.

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances (vancomycin, ciprofloxacin, and minocycline) an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible (S):**
A category defined by a breakpoint that implies that isolates with an MIC at or below the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Intermediate (I):**
A category defined by a breakpoint that includes isolates with MICs within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

**Resistant (R):**
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

**Epidemiological Cutoff Value (ECV):**
The MIC that separates microbial populations into those with and without acquired resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency. (Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. 30th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2020)

When an ECV is reported, the following comment will be included: "This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates [WITH/WITHOUT] acquired resistance; however, correlation with treatment outcome is unknown."

**Clinical References:**
2. CLSI: Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2019:3-5, 246
include isoniazid, rifampin, ethambutol, and pyrazinamide. Susceptibility testing of each M tuberculosis complex isolate against these first-line antimycobacterial agents is a key component of patient management. In vitro susceptibility testing methods are available to assess the susceptibility of M tuberculosis complex isolates to selected antimycobacterial agents. The Clinical Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of M tuberculosis complex susceptibility testing results. Current recommendations indicate that laboratories should use a rapid broth method in order to obtain M tuberculosis susceptibility data as quickly as possible to help guide patient management. Resistance, as determined by rapid testing, must be confirmed by another method or by another laboratory. This test uses an FDA-cleared commercial system for rapid broth susceptibility testing of M tuberculosis complex and assesses resistance to antimycobacterial drugs at the critical concentrations.

**Useful For:** Rapid, qualitative susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture. Affirming the initial choice of chemotherapy for M tuberculosis infections. Confirming the emergence of drug resistance. Guiding the choice of alternate agents for therapy for M tuberculosis infections.

**Interpretation:** Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to the aforementioned drugs at the critical concentrations. Some experts believe that patients infected with strains exhibiting resistance to low levels of isoniazid (0.1 mcg/mL) but not exhibiting resistance to high levels (0.4 mcg/mL) may benefit from continuing therapy with this agent. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate therapeutic regimen and dosages.

**Reference Values:**
Results are reported as susceptible or resistant.

**Clinical References:**

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**MMLN5 82019**

**Antimicrobial Susceptibility, Nocardia species and other Aerobic Actinomycetes, Varies**

**Clinical Information:** Nocardia species and other aerobic actinomycetes can cause significant disease, often in immunocompromised patients. Clinical presentation can include, but is not limited to, pneumonia, skin abscess, bacteremia, brain abscess, eye infection, and joint infection. Antimicrobial susceptibility testing may aid with selection of appropriate antimicrobial agents for patient care.

**Useful For:** Determining the resistance of species of Nocardia and other aerobic actinomycetes to antimicrobial agents

**Interpretation:** Interpretive values for susceptibility testing of Nocardia species using a broth microdilution method are included in the report, as appropriate. For Rhodococcus equi, the interpretive values for vancomycin and rifampin will also be included. See Reference Values for additional information.

**Reference Values:**

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Concentration range mcg/mL</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S</td>
</tr>
</tbody>
</table>

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Antimycin, Blood

**Clinical Information:** Antimycin is a silvery white metal that is used in alloys for lead batteries, solder, sheet metal, bearings, castings, ammunition, and pewter. It is also used for pigments, abrasives, flame-proofing fabrics, and in medications (ie, sodium stibogluconate [Pentostam], which is used to treat cutaneous leishmaniasis).(1) Antimycin typically enters the environment during mining, processing of ores, emissions from coal-burning power plants, and production of alloys. Exposure to antimycin can occur through inhalation, ingestion, or dermal contact with soil, water, foods, or medications that contain it. In the workplace, exposure is usually via inhalation. OSHA has set a limit of 0.5 mg/m³ of antimycin in workroom air to protect workers during an 8-hour work shift (40-hour workweek).(2) Absorption of antimycin through the lungs may take days to weeks. Absorption of antimycin from ingestion typically enters the blood within a few hours.(2) The amount and form of the antimycin affects how much is absorbed. Once in the blood, antimycin is distributed to the liver, lungs, intestines, and spleen. Elimination is primarily through the urine, occurring over several weeks. The half-life varies depending on the chemical form. Trivalent antimycin is primarily bound to erythrocytes, while pentavalent antimycin is primarily found in plasma, which makes whole blood the preferred specimen to analyze for acute intoxication. Whole blood concentrations in healthy subjects not exposed to antimycin averaged 0.7 mcg/L and usually don't exceed 2 mcg/L.(3) In battery plant workers, median blood antimycin concentrations of 2.6 mcg/L were found in metal casters and 10 mcg/L in metal formers.(4) The effects of acute or chronic antimycin poisoning are similar to arsenic and include abdominal pain, dyspnea, nausea, vomiting, dermatitis, and visual disturbances.(1) Additionally, toxicity can include pneumoconiosis, and altered electrocardiograms.(2)

**Useful For:** Determining antimycin toxicity

**Interpretation:** Normal blood concentrations are 0.7-2 ng/mL in the unexposed, and 2.6-10 ng/mL in exposed workers.(3)
Antimony, Urine

Reference Values:
- Reference Range: <1.0 ng/mL

Clinical References:
5. Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

Antimullerian Hormone, Serum

Clinical Information:
Antimullerian hormone (AMH), also known as mullerian-inhibiting substance, is a dimeric glycoprotein hormone belonging to the transforming growth factor-beta family. It is produced by Sertoli cells of the testis in males and by ovarian granulosa cells in females.

Expression during male fetal development prevents the mullerian ducts from developing into the uterus, resulting in development of the male reproductive tract. In the absence of AMH, the mullerian ducts and structures develop into the female reproductive tract. AMH serum concentrations are elevated in males under 2 years old and then progressively decrease until puberty, when there is a sharp decline. In females, serum AMH concentrations are very low at birth, peaking after puberty, decrease progressively thereafter with age, and become undetectable at menopause. Because of the gender differences in AMH concentrations, its changes in circulating concentrations with sexual development, and its specificity for Sertoli and granulosa cells, measurement of AMH has utility in the assessment of gender, gonadal function, fertility, and as a gonadal tumor marker. In females, AMH is considered an ovarian reserve marker. It correlates with the primordial follicle pool, has an inverse correlation with chronologic age, predicts ovarian response in assisted reproductive therapy, and has been suggested to be predictive of the timing of the onset of menopause. In contrast to other markers of ovarian reserve that show significant fluctuations during the menstrual cycle, serum AMH concentrations have been shown to be relatively stable. Females with higher concentrations of AMH have a better response to ovarian stimulation and tend to produce more retrievable oocytes than females with low or undetectable AMH.

Females at risk of ovarian hyperstimulation syndrome after gonadotropin administration can have significantly elevated AMH concentrations. Polycystic ovarian syndrome can elevate serum AMH concentrations because it is associated with the presence of large numbers of small follicles. AMH measurements are commonly used to evaluate testicular presence and function in infants with intersex conditions or ambiguous genitalia and to distinguish between cryptorchidism and anorchia in males.

Serum AMH concentrations are increased in some patients with ovarian granulosa cell tumors, which comprise approximately 10% of ovarian tumors. AMH, along with related tests including inhibin A and B (INHA / Inhibin A, Tumor Marker, Serum; INHB / Inhibin B, Serum; INHAB / Inhibin A and B, Tumor Marker, Serum), estradiol (EEST / Estradiol, Serum), and cancer antigen 125 (CA25 / Cancer Antigen 125 [CA 125], Serum), can be useful for diagnosing and monitoring these patients.

Useful For:
- Assessing ovarian status, including ovarian reserve and ovarian responsiveness, as part of an evaluation for infertility and assisted reproduction protocols
- Assessment of menopausal status
- Evaluation of infants with ambiguous genitalia and other intersex conditions
- Evaluating testicular function in infants and children
- Monitoring patients with antimullerian hormone-secreting ovarian granulosa cell tumors

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Interpretation: Menopausal women or women with premature ovarian failure of any cause, including after cancer chemotherapy, have very low antimullerian hormone (AMH) levels. While the optimal AMH concentrations for predicting response to in vitro fertilization are still being established, it is accepted that AMH concentrations in the perimenopausal to menopausal range indicate minimal to absent ovarian reserve. Depending on patient age, ovarian stimulation is likely to fail in such patients. AMH may be used as a surrogate to antral follicle count (AFC) at day 2 to 4 of the menstrual cycle to determine ovarian reserve. Women with an AFC greater than 15 are identified as having high ovarian reserve. In this context a Roche AMH concentration greater than 1.77 ng/mL at day 2 to 4 of the menstrual cycle, identified women with an AFC greater than 15 with 88.3% sensitivity and 68.3% specificity.(1) Controlled ovarian stimulation (COS) with exogenous gonadotropin is an essential step of in-vitro fertilization (IVF) protocols. Using the Roche AMH assay, a cut-off of 2.10 ng/mL is correlated with the response categories in women undergoing COS using a gonadotropin-releasing hormone antagonist protocol. A 2.10 ng/mL cutoff provided reliable prediction of hyper-response to COS(2). Sensitivity for the detection of hyperresponsive individuals was 81.3%, and the negative predictive value for ruling out hyperresponse was 96.6%. The 2.10 ng/mL cutoff identified 88.9% of patients with a poor response.(2) In patients with polycystic ovarian syndrome, AMH concentrations may be 2- to 5-fold higher than age-appropriate reference range values. Such high levels predict anovulatory and irregular cycles. In children with intersex conditions, an AMH result above the normal female range is predictive of the presence of testicular tissue, while an undetectable value suggests its absence. In boys suspected of cryptorchidism, a measurable AMH concentration is predictive of undescended testes, while an undetectable value is highly suggestive of anorchia or functional failure. Klinefelter syndrome is characterized by accelerated germ cell depletion and occurs in approximately 10% to 12% of men presenting with nonobstructive azoospermia. In these patients, serum AMH concentrations are within the reference interval until puberty and thereafter, AMH concentrations decline to abnormally low or undetectable. Pubertal delay and congenital hypogonadotropic hypogonadism (HH) share the same clinical manifestation of delayed sexual maturation in prepubertal boys. Levels of gonadotropin and testosterone are very low in prepubertal boys and therefore have little clinical significance; thus, AMH measurements are useful in the differential diagnosis of pubertal delay and congenital HH. In patients with congenital HH, AMH concentrations are abnormally low; while in pubertal delay AMH concentrations will be within the prepubertal reference interval. Granulosa cell tumors of the ovary may secrete AMH, inhibin A, and inhibin B. Elevated levels of any of these markers can indicate the presence of such a neoplasm in a woman with an ovarian mass. Levels should fall with successful treatment. Rising levels indicate tumor recurrence or progression.

Reference Values:

Males
<2 years: 18-283 ng/mL
2-12 years: 8.9-109 ng/mL
>12 years: <13 ng/mL

Females
<3 years: 0.11-4.2 ng/mL
3-6 years: 0.21-4.9 ng/mL
7-11 years: 0.36-5.9 ng/mL
12-14 years: 0.49-6.9 ng/mL
15-19 years: 0.62-7.8 ng/mL
20-24 years: 1.2-12 ng/mL
25-29 years: 0.89-9.9 ng/mL
30-34 years: 0.58-8.1 ng/mL
35-39 years: 0.15-7.5 ng/mL
40-44 years: 0.03-5.5 ng/mL
45-50 years: <2.6 ng/mL
51-55 years: <0.88 ng/mL
>55 years: <0.03 ng/mL


VASC

Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum

Clinical Information: Antineutrophil cytoplasmic antibodies (ANCA) occur in patients with autoimmune vasculitis including Wegener granulomatosis (WG), microscopic polyangiitis (MPA), or organ-limited variants thereof such as pauci-immune necrotizing glomerulonephritis.(1) ANCA react with enzymes in the cytoplasmic granules of human neutrophils including proteinase 3 (PR3), myeloperoxidase (MPO), elastase, and cathepsin G. Autoantibodies to PR3 occur in patients with WG (both classical WG and WG with limited end-organ involvement) and produce a characteristic pattern of granular cytoplasmic fluorescence on ethanol-fixed neutrophils called the cANCA pattern. Antibodies to MPO occur predominately in patients with MPA and produce a pattern of perinuclear cytoplasmic fluorescence on ethanol-fixed neutrophils called the pANCA pattern. Autoantibodies to PR3 and MPO can also be detected by EIA methods and are referred to as PR3 ANCA and MPO ANCA, respectively.

Useful For: Evaluating patients suspected of having autoimmune vasculitis, both Wegener granulomatosis and microscopic polyangiitis

Interpretation: Positive results for proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCA) and cANCA or pANCA are consistent with the diagnosis of Wegener granulomatosis (WG), either systemic WG with respiratory and renal involvement or limited WG with more restricted end-organ involvement. Positive results for MPO ANCA and pANCA are consistent with the diagnosis of autoimmune vasculitis including microscopic polyangiitis (MPA) or pauci-immune necrotizing glomerulonephritis. A positive result for PR3 ANCA or MPO ANCA has been shown to detect 89% of patients with active WG or MPA (with or without renal involvement) with fewer than 1% false-positive results in patients with other diseases.(1)

Reference Values:

MYELOPEROXIDASE ANTIBODIES, IgG
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.

PROTEINASE 3 ANTIBODIES, IgG
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.


ANA2

Antinuclear Antibodies (ANA), Serum

Clinical Information: Measurement of antinuclear antibodies (ANA) in serum is the most
commonly performed screening test for patients suspected of having a systemic rheumatic disease, also referred to as connective tissue disease. (1) ANA occur in patients with a variety of autoimmune diseases, both systemic and organ-specific. They are particularly common in the systemic rheumatic diseases, which include lupus erythematosus (LE), discoid LE, drug-induced LE, mixed connective tissue disease, Sjögren syndrome, scleroderma (systemic sclerosis), CREST (calcinosis, Raynaud phenomenon, esophageal dystmotility, sclerodactyly, telangiectasia) syndrome, polymyositis/dermatomyositis, and rheumatoid arthritis. (1) The diagnosis of a systemic rheumatic disease is based primarily on the presence of compatible clinical signs and symptoms. The results of tests for autoantibodies including ANA and specific autoantibodies are ancillary. Additional diagnostic criteria include consistent histopathology or specific radiographic findings. Although individual systemic rheumatic diseases are relatively uncommon, a great many patients present with clinical findings that are compatible with a systemic rheumatic disease and large numbers of tests for ANA are ordered to eliminate the possibility of a systemic rheumatic disease. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients suspected of having a systemic rheumatic disease

**Interpretation:** A large number of healthy individuals have weakly-positive antinuclear antibody (ANA) results, many of which are likely to be clinical false-positives; therefore, second-order testing of all positive ANA yields a very low percentage of positive results to the specific nuclear antigens. A positive ANA result at any level is consistent with the diagnosis of systemic rheumatic disease, but a result greater than or equal to 3.0 U is more strongly associated with systemic rheumatic disease than a weakly-positive result. Positive ANA results greater than 3.0 U are associated with the presence of detectable autoantibodies to specific nuclear antigens. The nuclear antigens are associated with specific diseases (eg, anti-Scl 70 is associated with scleroderma) and can be detected with second-order testing.

**Reference Values:**
- <or =1.0 U (negative)
- 1.1-2.9 U (weakly positive)
- 3.0-5.9 U (positive)
- >or =6.0 U (strongly positive)

Reference values apply to all ages.

results, many of which are likely to be clinical false-positives; therefore, second-order testing of all positive ANAs yields a very low percentage of positive results to the specific nuclear antigens. A positive ANA result at any level is consistent with the diagnosis of systemic rheumatic disease. Positive ANA results are associated with the presence of detectable autoantibodies to specific nuclear antigens. The nuclear antigens are associated with specific diseases (e.g., anti-Scl 70 is associated with scleroderma) and can be detected with second-order testing.

**Reference Values:**
<1:80 (Negative)


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**Antistrep-O Titer, Serum**

**Clinical Information:** A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

**Useful For:** Demonstration of acute or recent streptococcal infection

**Interpretation:** Elevated values are consistent with an antecedent infection by group A streptococci.

**Reference Values:**
- <5 years: < or =70 IU/mL
- 5-17 years: < or =640 IU/mL
- > or =18 years: < or =530 IU/mL


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**Antithrombin Activity, Plasma**

**Clinical Information:** Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa. (1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance the anticoagulant activity of antithrombins (approximately 1000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of anticoagulant activity of heparin. The antithrombin gene on chromosome 1 encodes a glycoprotein with a molecular weight of approximately 58,000 Da that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcmol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin
activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]) with the potential of development as early as adolescence or younger adulthood. More than 100 different genetic alterations have been identified throughout the gene producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen). (2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2000 to 1:3000 in general populations, although minor deficiency (antithrombin activity =70%-75%) may be more frequent (approximately 1:350-650). In populations with venous thrombophilia, approximately 1% to 2% of individuals have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C [APC]-resistance [factor V Leiden variant]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (e.g., stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS). (3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF), disseminated intravascular coagulation (DIC), or other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) or with nephritic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions (1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) is being evaluated. (4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

**Useful For:** Diagnosis of antithrombin deficiency, acquired or congenital Monitoring treatment of antithrombin deficiency disorders, including infusion of antithrombin therapeutic concentrate

**Interpretation:** Antithrombin deficiencies due to inherited causes are much less common than those due to acquired causes (see Clinical Information). Diagnosis of hereditary deficiency requires clinical correlation, with the prospect of repeat testing (including antithrombin antigen assay), and family studies (with appropriate counseling). DNA-based diagnostic testing may be helpful, see ATNGS / Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies. The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations. (4) Antithrombin deficiency, acquired or congenital, may contribute to the phenomenon of "heparin therapy resistance" (requirement of larger heparin doses than expected for achievement of therapeutic anticoagulation responses). However, it may more often have other pathophysiology, such as "acute-phase" elevation of coagulation factor VIII or plasma heparin-binding proteins. Increased antithrombin activity is of unknown hemostatic significance. Direct factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) may falsely elevate the antithrombin activity and mask a diagnosis of antithrombin deficiency.

**Reference Values:**
Normal values: 80-130%
Normal, full-term newborn infants have lower levels (> or =35-40%) that reach normal values by age 90 days. Premature infants (30-36 weeks gestation) have lower levels that reach normal values by age 180 days.

Antithrombin Antigen, Plasma

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance antithrombin's anticoagulant activity (approximately 1,000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of heparin's anticoagulant activity. The antithrombin gene on chromosome 1 encodes a glycoprotein of approximately 58,000 molecular weight that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcmol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare, autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism), with the potential of development as early as adolescence or younger adulthood. More than 100 different mutations have been identified throughout the gene, producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2,000 to 1:3,000 in general populations, although minor deficiency (antithrombin activity =70% to 75%) may be more frequent (approximately 1:350 to 1:650). In populations with venous thrombophilia, approximately 1% to 2% have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C: APC-resistance [factor V Leiden mutation]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) -Nephrotic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe DIC/IFC is being evaluated.(4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

Useful For: Assessing abnormal results of the antithrombin activity assay (ATTF / Antithrombin Activity, Plasma), which is recommended as the primary (screening) antithrombin assay Diagnosing antithrombin deficiency, acquired or congenital, in conjunction with measurement of antithrombin activity An adjunct in the diagnosis and management of carbohydrate-deficient glycoprotein syndromes

Interpretation: Hereditary antithrombin deficiency is much less common than acquired deficiency. Diagnosis of hereditary deficiency requires clinical correlation, testing of both antithrombin activity and antithrombin antigen, and may be aided by repeated testing and by family studies. DNA-based diagnostic testing may be helpful, but is generally not readily available. Acquired antithrombin deficiency may occur in association with a number of conditions (see Clinical Information). The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations.(4) Increased antithrombin activity has no definite clinical significance.
Reference Values:
Adults: 80-120%
Normal, full-term newborn infants may have decreased levels (> or =35-40%), which reach adult levels by 180 days postnatal.*
Healthy, premature infants (30-36 weeks gestation) may have decreased levels, which reach adult levels by 180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.


ATNGS 606366
Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies

Clinical Information: Antithrombin (AT) deficiency is a rare hereditary thrombophilia that puts patients at a significantly increased risk of venous thromboembolism. In selected cases, patients manifest heparin resistance. Individuals with AT deficiency are at increased risk for venous thromboembolism (VTE) and late (2nd or 3rd trimester) pregnancy loss.(1,2) It has been estimated that individuals with inherited AT deficiency have a 16-fold increase in risk of VTE compared to individuals without AT deficiency.(4) Women with AT deficiency are at particularly high risk for developing clots during pregnancy and after delivery.(5) Hereditary AT deficiency is uncommon, with prevalence in the general population of 1 in 2000 to 5000.(1, 2) Hereditary AT deficiency is inherited in an autosomal dominant manner with variable penetrance. Both men and women may be affected. AT deficiency is a result of defects in the concentration or function of AT, a natural anticoagulant in blood plasma. AT is the major inhibitor of blood coagulation by inactivating thrombin and factor Xa. The SERPINC1 gene encodes for antithrombin. Genetic testing of SERPINC1 is indicated if plasma AT activity assay is abnormally low (ie, typically less than 80% of normal or lower than the reference range established in the local laboratory). AT activity testing should not be performed during acute thrombosis or illness as these could cause a temporary reduction in AT levels. Likewise, it should not be performed while the patient is taking an anticoagulant such as heparin (which may falsely lower levels) or an oral direct factor Xa inhibitor (eg, rivaroxaban, apixaban or edoxaban), which may falsely elevate AT levels. Additionally, causes of acquired (non-genetic) AT deficiency are much more common than inherited AT deficiency and should be excluded prior to genetic testing. These causes of acquired AT deficiency include liver disease, acute thrombosis, heparin therapy, nephrotic syndrome, disseminated intravascular coagulation, and effects of chemotherapeutic agents such as L-asparaginase. These and other acquired causes of AT deficiency should be excluded prior to genetic testing.

Useful For: Ascertainment of a causative alteration in SERPINC1 and the affected region of antithrombin (AT) protein in an individual clinically diagnosed with antithrombin deficiency Genetic confirmation of a clinical AT deficiency diagnosis, particularly in patients with borderline low AT activity levels Prognosis and risk assessment based on the genotype-phenotype correlations Ascertainment alteration status of family members related to an individual with a confirmed SERPINC1 alteration for the purposes of informing clinical management and genetic counseling Evaluating individuals with apparent heparin resistance This test is not intended for prenatal diagnosis

Interpretation: An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, and Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Reference Values:
An interpretive report will be provided


**APCZ 35418**

**APC Gene, Full Gene Analysis, Varies**

**Clinical Information:** Familial adenomatous polyposis (FAP) is an autosomal dominant condition caused by alterations in the APC gene located on the long arm of chromosome 5 (5q21). Classic FAP is characterized by progressive development of hundreds to thousands of adenomatous colon polyps. Polyps may develop during the first decade of life, and the majority of untreated FAP patients will develop colon cancer by age 40. Typically, there is a predominance of polyps on the left side of the colon; however, other areas of the colon may also be affected. The presence of extracolonic manifestations is variable and includes gastric and duodenal polyps, ampullary polyps, osteomas, dental abnormalities (unerupted teeth), congenital hypertrophy of the retinal pigment epithelium (CHRPE), benign cutaneous lesions, desmoids tumors, hepatoblastoma, and extracolonic cancers. Common constellations of colonic and extracolonic manifestations have resulted in the designation of 3 clinical variants: Gardner syndrome, Turcot syndrome, and hereditary desmoid disease. Gardner syndrome is characterized by colonic polyps of classic FAP with epidermoid skin cysts and benign ostoid tumors of the mandible and long bones. Turcot syndrome is characterized by multiple colonic polyps and central nervous system (CNS) tumors. Turcot syndrome is an unusual clinical variant of FAP, as it is also considered a clinical variant of hereditary nonpolyposis colorectal cancer (HNPCC). Individuals with Turcot syndrome have CNS tumors in addition to adenomatous polyps. The types of CNS tumor observed helps to distinguish Turcot-FAP variant patients from Turcot-HNPCC variant patients. The predominant CNS tumor associated with the Turcot-FAP variant is medulloblastoma, while glioblastoma is the predominant CNS tumor associated with Turcot-HNPCC. Hereditary desmoid disease (HDD) is a variant of FAP with multiple desmoids tumors as the predominant feature. Many patients with HDD may not even show colonic manifestations of FAP. APC germline testing may assist clinicians in distinguishing a sporadic desmoid tumor from that associated with FAP. Attenuated FAP (AFAP) is characterized by later onset of disease and a milder phenotype (typically <100 adenomatous polyps and fewer extracolonic manifestations) than classic FAP. Typically individuals with AFAP develop symptoms of the disease at least 10 to 20 years later than classically affected individuals. Individuals with AFAP often lack a family history of colon cancer and/or multiple adenomatous polyps.

Useful For: Confirmation of familial adenomatous polyposis (FAP) diagnosis for patients with clinical features

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

**Reference Values:**
An interpretive report will be provided.


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**APIXA 65848**

**Apixaban, Anti-Xa, Plasma**

**Clinical Information:** Apixaban, an oral anticoagulant that directly inhibits factor Xa, has been approved by the FDA for prophylaxis of thrombosis in atrial fibrillation and surgical patients and treatment of venous thromboembolism (VTE). Unlike warfarin, it does not require routine therapeutic monitoring. However, in selected clinical situations, measurement of drug level would be useful (eg, renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight). Predicted Apixaban Steady-state Exposure Concentrations(1) Apixaban C-min (ng/mL) trough plasma conc (predose) Apixaban C-max (ng/mL) peak plasma conc (2-4 hours postdose) Prevention of VTE: elective hip or knee replacement surgery 2.5 mg twice daily 51 (23-109) 77 (41-146) Prevention of stroke and systemic embolism: NVAF 2.5 mg twice daily 79 (34-162) 123 (69-221) 5 mg twice daily 103 (41-230) 171 (91-321) Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE) 2.5 mg twice daily 32 (11-90) 67 (30-153) 5 mg twice daily 63 (22-77) 132 (59-302) 10 mg twice daily 120 (41-335) 251 (111-572) Median (5th-95th percentile) VTE-venous thromboembolism, NVAF- nonvalvular atrial fibrillation, DVT-deep vein thrombosis, PE-pulmonary embolism

**Useful For:** Measuring apixaban concentration in selected clinical situations (eg, renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age and extremes of body weight)

**Interpretation:** The lower limit of detection of this assay is 10 ng/mL. Therapeutic reference ranges have not been established. See Clinical Information section for peak and trough drug concentrations observed from clinical trials.

**Reference Values:**
<10 ng/mL

Apixaban, Plasma

**Interpretation:** In a study of 1691 patients taking apixaban, doses ranging from 2.5 mg twice a day to 20 mg once a day, apixaban plasma concentrations ranged from 1 to 933 ng/mL, with a median value of 105 ng/mL.

**Reference Values:**
Reporting limit determined each analysis.

Mean peak plasma concentrations of apixaban following a single oral administration of 5, 10, 25, or 50 mg oral tablets are as follows:

- 5 mg: 104.7 ng/mL (range, 79.7 to 129.7)
- 10 mg: 176.3 ng/mL (range, 134.3 to 218.3)
- 25 mg: 365.1 ng/mL (range, 348.1 to 382.1)
- 50 mg: 685.2 ng/mL (range, 663.2 to 707.2)

APOL1 Genotype, Varies

**Clinical Information:** The APOL1 gene encodes apolipoprotein L-1, a serum apolipoprotein bound to high-density lipoprotein (HDL) particles. Two alleles, commonly called G1 and G2, have been associated with increased risk for development or progression of nondiabetic chronic kidney diseases, including HIV-associated nephropathy (HIVAN), primary focal segmental glomerulosclerosis (FSGS), and lupus-associated collapsing glomerulopathy.(1-4) The G1 allele is a haplotype consisting of 2 missense variants: c.1024A>G (p.Ser342Gly) and c.1152T>G (p.Ile384Met). The G2 allele is comprised of a 6 base pair deletion that results in the deletion of 2 amino acids: c.1164_1169delTTATAA (p.Asn388_Tyr389del). The G1 and G2 alleles are thought to be in complete linkage disequilibrium, meaning when both the G1 and G2 alleles are detected, they are on opposite chromosomes.(1) Risk for chronic kidney disease is only increased when 2 risk alleles are inherited (ie, genotypes G1/G1, G2/G2, or G1/G2), following an autosomal recessive pattern of inheritance.(1)

Individuals with one risk allele or no risk alleles do not appear to be at an increased risk. The G1 and G2 risk alleles are enriched in individuals of African ancestry. Population studies show that in individuals of African descent, the G1 allele is found on 20% to 22.5% of chromosomes, and the G2 allele is found on 13% to 15% of chromosomes.(5-6) More importantly, it is estimated that 10% to 15% of individuals of African descent carry 2 risk alleles.(5-6) The high frequency of the G1 and G2 alleles in this population is likely due to the protective effect these alleles confer against Trypanosoma rhodesiense, a parasite that causes trypanosomiasis, a disease endemic to Africa.(1) The G1 and G2 alleles are extremely rare or absent in individuals not of recent African descent (eg, European and Asian descent).(1,5) For this reason, increased risk associated with the G1 and G2 alleles has only been stratified in populations of recent African ancestry, and it remains unclear if similar risk effects associated with the APOL1 risk genotypes are applicable to individuals without African ancestry. Currently, there are no guidelines for clinical management of individuals with APOL1 risk genotypes. Evidence exists that the donor APOL1 genotype may impact both donor and recipient outcomes of kidney allografts. Results from 2 studies have shown that donor kidneys from individuals with 2 risk alleles were more likely to fail after transplantation when compared to donor kidneys from individuals with one or no risk alleles.(7-8) Another study suggests that living donors with two risk alleles may be at an increased risk for reduced kidney function following kidney donation.(9) At this time, there has been no association between the genotype of the allograft recipient and transplant outcomes, suggesting that allograft recipients with two risk alleles have similar outcomes to recipients with one or no risk alleles.(10) However, a prospective, large scale study to assess kidney allograft survival from donors with recent African ancestry based on donor and recipient APOL1 genotypes is currently ongoing.(11) Based on presently available data, guidelines advise that an individual’s APOL1 genotype alone should not determine eligibility for donation or receipt of kidney allografts.(12)

Useful For: Determining an individual’s APOL1 genotype. This test is not useful for clinical management of individuals with APOL1 risk genotypes. This test alone is not useful for determining eligibility for donation or receipt of kidney allografts.
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**APO1Z**

**Apolipoprotein A-I (APOA1) Gene, Full Gene Analysis, Varies**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein A-I, apolipoprotein A-II, fibrinogen alpha chain, gelsolin, cystatin C, and lysozyme. Apolipoprotein A-I, apolipoprotein A-II, lysozyme, and fibrinogen alpha-chain amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Apolipoprotein A-I amyloidosis is also associated with additional organ system involvement, including clinical manifestations in the liver, heart, skin, and larynx. In addition, the G26R APOA1 mutation has been described with a neuropathic presentation. To date, at least 16 amyloidogenic mutations have been identified within the APOA1 gene. The majority of these are missense mutations, although deletion/insertion mutations have also been described. There is some evidence of genotype-phenotype correlations. Mutations that occur near the amino terminal portion of the protein are more often associated with hepatic and renal amyloidosis, while mutations occurring near the carboxyl terminal portion of the gene are more often associated with cardiac, cutaneous, and laryngeal amyloidosis. The majority of mutations reported to date occur at 1 of 2 hot spots spanning amino acid residues 50 through 93 and 170 through 178. Mutations in the APOA1 gene have also been linked to familial hypoalphalipoproteinemia. Patients carrying 1 APOA1 mutation typically demonstrate reduced levels of high-density lipoprotein (HDL) cholesterol, which is...
associated with increased risk for coronary artery disease. Comparatively, the presence of 2 APOA1 mutations generally results in complete absence of HDL cholesterol and may include additional clinical features such as xanthomas or corneal opacities. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnosis of individuals suspected of having apolipoprotein A-I (APOA1) gene-associated familial amyloidosis

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**APO2Z**

**Apolipoprotein A-II (APOA2) Gene, Full Gene Analysis, Varies**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis, including those that encode transthyretin, apolipoprotein A-I, apolipoprotein A-II, fibrinogen alpha chain, gelsolin, cystatin C, and lysozyme. Apolipoprotein A-I, apolipoprotein A-II, lysozyme, and fibrinogen alpha chain amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Apolipoprotein A-II amyloidosis typically presents as a very slowly progressive disease. Age of onset is highly variable, ranging from adolescence to the fifth decade. To date, all mutations that have been identified within the APOA2 gene occur within the stop codon and result in a 21-residue C-terminal extension of the apolipoprotein A-II protein. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnosis of individuals suspected of having apolipoprotein A-II-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.


ApoA1 and B, Serum

Clinical Information: Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). Apolipoprotein A1 (ApoA1) is the primary protein component of high-density lipoprotein (HDL). Elevated ApoB and decreased ApoA1 are associated with increased risk of cardiovascular disease. Multiple studies have reported that ApoB and ApoA1 are more strongly associated with cardiovascular disease than the corresponding lipoprotein cholesterol fraction (see APOA1 / Apolipoprotein A1, Serum and APOLB / Apolipoprotein B, Serum). ApoB is present in all atherogenic lipoproteins including LDL, Lp(a), intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL) remnants. ApoA1 is the nucleating protein around which HDL forms during reverse cholesterol transport. The ApoB:ApoA1 ratio represents the balance between atherogenic and antiatherogenic lipoproteins. Several large prospective studies have shown that the ApoB:ApoA1 ratio performs as well, and often better, than traditional lipids as an indicator of risk.(1-3)

Useful For: Assessment of cardiovascular risk Follow-up studies in individuals with basic lipid measures inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors

Interpretation: Elevated apolipoprotein B (ApoB) confers increased risk of atherosclerotic cardiovascular disease, even in a context of acceptable LDL cholesterol concentrations. Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy. Reduced apolipoprotein A1 (ApoA1) confers an increased risk of coronary artery disease. Extremely low ApoA1 (<20 mg/dL) is suggestive of liver disease or a genetic disorder. Elevated ApoB:ApoA1 ratio confers increased risk of atherosclerotic cardiovascular disease, independently of LDL and HDL cholesterol concentrations.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
<th>Apolipoprotein B (mg/dL)</th>
<th>Apolipoprotein B/A1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td>Not established</td>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120</td>
<td>Acceptable: high: 90-109</td>
<td>Lower Risk: Risk: 0.7-0.9</td>
</tr>
<tr>
<td></td>
<td>&gt;120</td>
<td></td>
<td>Higher Risk: &gt;0.9 Females</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>&gt; or =120</td>
<td>Desirable: Desirable: 90-99</td>
<td>0.7-0.9 Females</td>
</tr>
<tr>
<td></td>
<td>Borderline high: 100-119</td>
<td>Very high: &gt; or =140</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Apolipoprotein A (mg/dL)</td>
<td>Apolipoprotein B (mg/dL)</td>
<td>Apolipoprotein B/A1 ratio</td>
</tr>
<tr>
<td>Not established</td>
<td>Not established</td>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120</td>
<td>Acceptable: high: 90-109</td>
<td>Lower Risk: Risk: 0.7-0.9</td>
</tr>
<tr>
<td></td>
<td>&gt;120</td>
<td></td>
<td>Higher Risk: &gt;0.9 Females</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 230
**Clinical References:**

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**APOA1**

**Apolipoprotein A1, Serum**

**Clinical Information:** Apolipoprotein A1 (ApoA1) is the primary protein associated with high-density lipoprotein (HDL) particles, and plays a central role in reverse cholesterol transport.(1) HDL cholesterol (HDL-C) and ApoA1 concentrations are inversely related to the risk for coronary artery disease (CAD).(2) There are a variable number of ApoA1 proteins per HDL particle. Therefore, ApoA1 is not a 1:1 surrogate marker for HDL particles. Similarly, the number of ApoA1 proteins and the amount of cholesterol contained in HDL particles is highly variable. This heterogeneity has led to unique clinical findings related to ApoA1 compared with HDL-C. Increased ApoA1 concentrations are more strongly associated with a reduction in risk of a first myocardial infarction than HDL-C concentrations.(3) Low concentrations of ApoA1, but not HDL-C, are predictive of preclinical atherosclerosis as assed by computed tomography estimated coronary artery calcium (CAC) scoring.(4) Increased ApoA1, but not HDL-C concentrations, are associated with reduced cardiovascular events among statin-treated patients, even when LDL-C <50 mg/dL.(5) In statin-treated patients, patients whose ApoA1 increased while on treatment were at lower risk than those whose ApoA1 did not increase.

**Useful For:** Evaluating risk for atherosclerotic cardiovascular disease Aiding in the detection of Tangier disease

**Interpretation:** Low levels of apolipoprotein A1 (ApoA1) confer increased risk of atherosclerotic cardiovascular disease. ApoA1 below 25 mg/dL may aid in the detection of a genetic disorder such as Tangier disease. ApoA1 is often interpreted as a ratio with apolipoprotein B (ApoB).

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120 Acceptable: &gt;120</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>&gt; or =120 Females</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120 Acceptable: &gt;120</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>&gt; or =140</td>
</tr>
</tbody>
</table>
**Clinical Information:** Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). The amount of cholesterol contained within LDL varies, but each LDL contains exactly 1 ApoB protein. Therefore, ApoB is a more reliable indicator of circulating LDL compared to LDL cholesterol (LDL-C). ApoB has been demonstrated to perform equally with LDL particles measured by nuclear magnetic resonance spectroscopy. (1) ApoB is strongly associated with increased risk of developing cardiovascular disease (CVD) and often outperforms LDL-C at predicting risk of coronary heart disease. (2-4) Patients with acceptable non-HDL-C (or LDL-C) but elevated ApoB remain at higher risk of developing CVD; conversely, patients with acceptably low ApoB but moderate non-HDL-C or LDL-C elevations are at a reduced risk for CVD. (5,6) Finally, in 7 different placebo-controlled randomized clinical trials, on-statin reduction of ApoB was more closely related to CVD risk reduction than non-HDL-C or LDL-C. (7)

**Useful For:** Assessment of cardiovascular risk Follow-up studies in individuals with basic lipid measures inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors Confirmation of suspected abetalipoproteinemia or hypobetalipoproteinemia

**Interpretation:** Elevated ApoB confers increased risk of atherosclerotic cardiovascular disease, even in a context of acceptable LDL cholesterol. Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein B (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Acceptable: high: 90-109 High: &gt; or =110</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>Desirable: Desirable: 90-99 Borderline high: 100-119 High: 120-139 Very high: &gt; or =140</td>
</tr>
</tbody>
</table>

**Clinical References:**


APOE Genotyping, Blood
Clinical Information: Apolipoproteins are structural constituents of lipoprotein particles that participate in lipoprotein synthesis, secretion, processing, and metabolism. Apolipoproteins have critical roles in blood lipid metabolism. Defects in apolipoprotein E (Apo E) are responsible for familial dysbetalipoproteinemia, or type III hyperlipoproteinemia, in which increased plasma cholesterol and triglycerides result from impaired clearance of chylomicron and very-low-density lipoprotein (VLDL) remnants. The human APOE gene is located on chromosome 19. The 3 common APOE alleles are designated e2, e3, and e4, which encode the Apo E isoforms E2, E3, and E4, respectively. E3, the most common isoform in Caucasians, shows cysteine (Cys) at amino acid position 112 and arginine (Arg) at position 158. E2 and E4 differ from E3 by single amino acid substitutions at positions 158 and 112, respectively (E2: Arg158->Cys; E4: Cys112->Arg). The allele frequencies for most Caucasian populations are as follows: -e2=8% to 12% -e3=74% to 78% -e4=14% to 15% E2 and E4 are both associated with higher plasma triglyceride concentrations. Over 90% of individuals with type III hyperlipoproteinemia are homozygous for the e2 allele. However, <10% of individuals homozygous for the e2 allele have overt type III hyperlipoproteinemia. This suggests that other genetic, hormonal, or environmental factors must contribute to the phenotypic expression of the disease. The e4 allele has been linked to pure elevations of low-density lipoproteins (LDL). Patients with a lipid profile consistent with type III hyperlipidemia are candidates for analysis of their APOE genotype. The APOE gene is also a known susceptibility gene for Alzheimer disease. The e4 allele is associated with an increased risk for Alzheimer disease, particularly late-onset disease, in a dose-dependent manner. This risk is also influenced by other factors. It is estimated that individuals with the APOE e3/e4 genotype have a 4-fold relative risk for Alzheimer disease, while homozygotes for e4 allele have a 12-fold relative risk. Several studies have suggested a protective effect of the APOE e2 allele. The APOE e4 allele, however, is neither sufficient nor necessary for the development of Alzheimer disease. Approximately 50% of individuals with Alzheimer disease carry an e4 allele and many individuals who have an e4 allele will never develop Alzheimer disease. The use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

Useful For: Determining the specific apolipoprotein E (APOE) genotypes in patients with type III hyperlipoproteinemia APOE genotyping has been used to assess susceptibility for Alzheimer disease. However, the use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

Interpretation: An interpretive report will be provided.

FAPLG

Apple IgG

Interpretation:

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

APPL

Apple, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to apples Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
</tbody>
</table>
**Apricot, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to apricots Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Arbovirus Antibody Panel, IgG and IgM, Serum**

**Clinical Information:** California (LaCrosse) Virus: California (LaCrosse) virus is a member of the Bunyaviridae family and is one of the arthropod-borne encephalitides. It is transmitted by various Aedes
and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children less than 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days, and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals, it is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis: Areas of outbreaks of St. Louis encephalitis (SLE) since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough, followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis: The virus that causes western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease, with about 20% of cases under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults.

**Useful For:** Aiding the diagnosis of arboviral encephalitis (California [LaCrosse], St. Louis, eastern equine and western equine encephalitis)

**Interpretation:** In patients infected with these or related viruses, IgM class antibody is reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. A single serum specimen IgG of 1:10 or greater indicates exposure to the virus. A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection. In the United States, it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity.

**Reference Values:**

**CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY**

- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.
EASTERN EQUINE ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

ST. LOUIS ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

WESTERN EQUINE ENCEPHALITIS
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References:

Arbovirus Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: California (LaCrosse) Virus: California (LaCrosse) virus is a member of the Bunyaviridae family and it is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children younger than 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. An estimated 2% of patients have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low-prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals, and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis: Areas or outbreaks of St. Louis encephalitis (SLE) since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough, followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise,
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**Useful For:** Aiding in the diagnosis of arboviral encephalitis (California [LaCrosse], St. Louis, Eastern equine, and Western equine encephalitis)

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**

**CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY**

- IgG: <1:1
- IgM: <1:1

Reference values apply to all ages.

**EASTERN EQUINE ENCEPHALITIS ANTIBODY**

- IgG: <1:1
- IgM: <1:1

Reference values apply to all ages.

**ST. LOUIS ENCEPHALITIS ANTIBODY**

- IgG: <1:1
- IgM: <1:1

Reference values apply to all ages.

**WESTERN EQUINE ENCEPHALITIS**

- IgG: <1:1
- IgM: <1:1

Reference values apply to all ages.

**Clinical References:**

factor IIa may be more reliable. There are no clinical studies directly correlating argatroban concentration to clinical outcomes. The available data suggest that plasma concentrations of argatroban 1.2 to 2.3 mcg/mL correspond to an APTT ratio of 1.5 to 3.0.(1)

**Useful For:** Measuring argatroban concentration in plasma This assay is not useful for measurement of other direct thrombin inhibitors eg, dabigatran or bivalirudin.

**Interpretation:** Therapeutic reference ranges have not been established. See Clinical Information for activated partial thromboplastin time correlative information.

**Reference Values:**<0.10 mcg/mL

**Clinical References:**

**ARGIN 70359**

**Arginase-1 Immunostain, Technical Component Only**

**Clinical Information:** Arginase-1 is a urea cycle metalloenzyme specifically expressed in hepatocytes. This protein serves as a marker in the identification and differentiation of hepatocellular carcinoma within the context of an antibody panel.

**Useful For:** Identification and differentiation of hepatocellular carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FARI**

*57112*

**Aripiprazole (Abilify)**

**Reference Values:**

**Units:** ng/mL

Expected steady state plasma levels in patients receiving recommended daily dosages: 109.0 - 585.0 ng/mL

**ARVGP**

*63160*

**Arrhythmogenic Cardiomyopathy Multi-Gene Panel, Blood**

**Clinical Information:** The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). Arrhythmogenic right ventricular dysplasia (ARVD or AC), is characterized by breakdown of the myocardium and replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. The incidence of ARVC is approximately 1 in 1,000 to 1 in 2,500. Age of onset and severity are variable, but symptoms typically develop in adulthood. ARVC is present in 4% to 22% of athletes with sudden cardiac death, and there is some debate whether high-intensity endurance exercise may cause development of ARVC. ARVC is typically considered a disease of the desmosome, the structure that attaches heart muscle cells to one another. The desmosome provides strength to the muscle tissue and plays a role in signaling between neighboring cells. Variants in the genes associated with ARVC disrupt this function, causing detachment and death of myocardial cells when the heart muscle is under stress. Damaged myocardium is replaced with fat and scar tissue, eventually leading to structural and electrical abnormalities that can lead to arrhythmia. Inheritance of ARVC typically follows an autosomal dominant pattern of inheritance, and variants in DSC2, DSP, and PKP2 account for approximately half of the variants identified in ARVC. However, simultaneous testing of all known ARVC genes is recommended due to the potential for compound heterozygosity (biallelic variants on the same gene) or digenic heterozygosity (variants in 2 different genes). See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Arrhythmogenic Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD DSC2 Desmocollin AD, AR ARVC, ARVC + skin and hair findings DSG2 Desmoglein AD ARVC DSP Desmoplakin AD, AR ARVC, DCM, Carvajal syndrome JUP Junction plakoglobin AD, AR ARVC, Narxos disease LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy, ARVC (see OMIM for full listing) PKP2 Plakophilin 2 AD ARVC RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS TMEM43 Transmembrane protein 43 AD ARVC, EMD TTN Titin AD, AR HCM, DCM, ARVC, myopathy Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), catecholaminergic polymorphic ventricular tachycardia (CPVT), long QT syndrome (LQTS), autosomal dominant (AD), autosomal recessive (AR)

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary arrhythmogenic right ventricular cardiomyopathy (ARVC or AC) Establishing a diagnosis of ARVC or AC, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published
American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.

Clinical References:

ARSAZ
35362

ARSA Gene, Full Gene Analysis, Varies

Clinical Information: Metachromatic leukodystrophy (MLD) is a rare autosomal recessive condition caused by mutations in the arylsulfatase A (ARSA) gene. The incidence of MLD is approximately 1:40,000 to 1:160,000, and the estimated carrier frequency in the general population is 1:100 to 1:200. MLD is characterized by the accumulation of cerebroside sulfate, which causes progressive demyelination and the loss of white matter. There is a variable age of onset. In the early onset form, symptoms appear in the first 1 to 2 years of life and include deterioration of skills such as walking and speaking. In the juvenile form, symptoms can appear between 4 years of age and the age of sexual maturity, and can include a decline in school performance and behavioral problems. Adults can present with a decline in school or job performance, substance abuse, and emotional lability. The diagnosis is suspected in individuals with progressive neurologic dysfunction and molecular resonance imaging evidence of leukodystrophy. The ARSA gene is located on chromosome 22 and has 8 exons. The following 4 mutations, c.459+1G>A, c.1204+1G>A, p.Pro426Leu, and p.Ile179Ser, account for 25% to 50% of mutations in the central and western European populations. The presence of 2 of these mutations within the ARSA gene confirms a diagnosis of metachromatic leukodystrophy. The recommended first-tier tests to screen for MLD are biochemical tests that measure arylsulfatase A enzyme activity in leukocytes and urine: ARSAW / Arylsulfatase A, Leukocytes and ARSU / Arylsulfatase A, 24 Hour, Urine. Individuals with decreased enzyme activity are more likely to have 2 mutations in the ARSA gene identifiable by molecular gene testing. However, arylsulfatase A enzyme assays cannot distinguish between MLD and ARSA pseudodeficiency, a clinically benign condition that leads to low in vitro ARSA levels, but it is found in 5% to 20% of the normal population. Thus, the diagnosis of MLD must be confirmed by molecular analysis of the ARSA gene.

Useful For: Second-tier test for confirming a diagnosis of metachromatic leukodystrophy (MLD) based on clinical findings and low arylsulfatase A (ARSA) activity levels Carrier testing when there is a family history of MLD, but disease-causing mutations have not been previously identified

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

Reference Values:
An interpretive report will be provided.

Arsenic Occupational Exposure, Random, Urine

Clinical Information: Arsenic is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As3+/AsIII) and arsenate (As5+/AsV). Inorganic AsV is readily reduced to inorganic As(III) which is then primarily broken down to the less toxic methylated metabolites monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and if not disposed of properly may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

Useful For: Screening test for detection of occupational exposure to arsenic using random urine specimens

Interpretation: Mayo Clinic uses the American Conference of Governmental Industrial Hygienists (ACGIH) biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated arsenic forms) or the relatively non-toxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, AsIII and AsV) are found in the urine shortly after ingestion, whereas the less toxic methylated forms (MMA and...
DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary AsIII and AsV concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. After a seafood meal (seafood generally contains the nontoxic, organic form of arsenic (eg, arsenobetaine)), the urine output of arsenic may increase to over 300 mcg/24 hr, after which it will decline. This test can determine if you have been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in your body will affect your health.

Reference Values:
Only orderable as part of profile. For more information see:
ARSOR / Arsenic Occupational Exposure with Reflex, Random, Urine
HMSOR / Heavy Metal Occupational Exposure, with Reflex, Urine

Clinical References:

Arsenic Occupational Exposure, Random, Urine

Clinical Information:
Arsenic is a naturally occurring element that is widely distributed in the Earth’s crust. Arsenic is classified chemically as a metalloid, having properties of both a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+)/As[III]) and arsenate (As[5+)/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide
application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

**Useful For:** Screening test for detection of occupational exposure to arsenic in random urine specimens

**Interpretation:** Mayo Clinic uses the American Conference of Governmental Industrial Hygienists (ACGIH) biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated arsenic forms) or the relatively nontoxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsenic acid (MMA) and dimethylarsinic acid (DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

**Reference Values:**
Only orderable as part of profile. For more information see:
- ASUOE / Arsenic Occupational Exposure with Reflex, Random, Urine
- HMUOE / Heavy Metal Occupational Exposure, with Reflex, Random, Urine

**Clinical References:**

**ASUOE**

**Clinical Information:** Arsenic is a naturally occurring element that is widely distributed in the Earth’s crust. Arsenic is classified chemically as a metalloid, having properties of both a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with
these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III) which is then primarily broken down to the less toxic methylated metabolites, monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

**Useful For:** Preferred screening test for detection of occupational exposure to arsenic in random urine specimens

**Interpretation:** Mayo Clinic uses the American Conference of Governmental Industrial Hygienists (ACGIH) biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated arsenic forms) or the relatively nontoxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As[III] and As[V] concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

**Reference Values:**
Biological Exposure Indices (BEI): <35 mcg/L at end of work week

Arsenic Speciation, 24 Hour, Urine

Clinical Information: Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic inorganic forms are arsenite (As[3+)/As[III]) and arsenate (As[5+]/As[V]), and their partially detoxified metabolites are monomethylarsine (MMA) and dimethylarsine (DMA). As(III) is more toxic than As(V) and both are more toxic than MMA- and DMA. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As(III)-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the two most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats, such as meats from chickens that have been fed on seafood remnants, may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid renal clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours. For reporting purposes, the concentrations of the inorganic forms (As[3+] and As[V]) along with the methylated forms (MMA and DMA) will be summed and reported together as 'Inorganic' arsenic. This is consistent with how the biological exposure index (BEI) reference range is reported.

Useful For: Diagnosis of arsenic intoxication using 24 hour urine specimens

Interpretation: The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations of 20 mcg inorganic arsenic per liter or higher are considered toxic. There is no limit to the normal range for the organic forms of arsenic, since they are not considered to be toxic and are normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hours would be that more than 95% is present as the organic species from a dietary source, and less than 5% is present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in seafood. A normal value for blood arsenic does not exclude a finding of elevated urine inorganic arsenic due to the very short half-life of blood arsenic.

Reference Values:
TOXIC ARSENIC
<35 mcg/L
Reference values apply to all ages.

Arsenic Speciation Interpretive Information:
The toxic arsenic concentration represents the sum of the inorganic and methylated arsenic species. The reference value for toxic arsenic is <35 mcg/L. This value is based on the American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index (BEI), which does not include the non-toxic organic arsenic.

Clinical References: 1. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD:

**Arsenic Speciation, Random, Urine**

**Clinical Information:** Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic forms are the inorganic species of As(3+) (As-III), As(5+) (As-V), and their partially detoxified metabolites, monomethylarsine, and dimethylarsine. As-III is more toxic than As-V, and both are more toxic than mono- and dimethylarsine. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As-III-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats, such as meats from chickens that have been fed on seafood remnants, may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid renal clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours. For reporting purposes, the concentrations of the inorganic forms (As[3+] and As[5+]) along with the methylated forms (monomethylarsine and dimethylarsine) will be summed and reported together as 'Inorganic' arsenic. This is consistent with how the biological exposure index (BEI) reference range is reported.

**Useful For:** Diagnosis of arsenic intoxication in random urine specimens

**Interpretation:** The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations of 20 mcg inorganic arsenic per liter or higher are considered toxic. There is no limit to the normal range for the organic forms of arsenic, since they are not considered to be toxic and are normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hours would be that more than 95% is present as the organic species from a dietary source, and less than 5% is present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in seafood. A normal value for blood arsenic does not exclude a finding of elevated urine inorganic arsenic, due to the very short half-life of blood arsenic.

**Reference Values:**

- **TOXIC ARSENIC**
  - <35 mcg/L
  - Reference values apply to all ages.

Arsenic Speciation Interpretive Information:

- The toxic arsenic concentration represents the sum of the inorganic and methylated arsenic species.
- The reference value for toxic arsenic is <35 mcg/L. This value is based on the ACGIH Biological Exposure Index (BEI), which does not include the nontoxic organic arsenic.

Arsenic is a naturally occurring element that is widely distributed in the Earth’s crust. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As(3+)/As(III)) and arsenate (As(5+)/As(V)). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) expose is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arsensiasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

Useful For: Preferred screening test for detection of arsenic exposure using 24-hour urine specimens

Interpretation: Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated forms) or the relatively non-toxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As(III) and As(V)) are found in the urine shortly after ingestion, whereas the less toxic methylated forms (monomethylarsinic acid: MMA dimethylarsinic acid: DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. After a seafood meal (seafood generally contains the nontoxic, organic form of arsenic (eg, arsenobetaine), the urine output of arsenic may increase to over 300 mcg/24-hour specimen, after which it will decline. This test can determine if you have been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in your body will affect your health.
**Reference Values:**

0-17 years: not established
> or =18 years: <35 mcg/24 hour

**Clinical References:**

**Arsenic, Blood**

**Clinical Information:** Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(V), also denoted as As(V), the more toxic As(III), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(III) is oxidized to As(V) and then methylated to MMA and DMA. As a result of these detoxification steps, As(III) and As(V) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because if its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur.

**Useful For:** Detection of acute or very recent arsenic exposure Monitoring the effectiveness of therapy This test is not useful for evaluation of chronic arsenic exposure.

**Interpretation:** Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of <6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen.

**Reference Values:**

<13 ng/mL
Reference values apply to all ages.

Arseonic, Hair

Clinical Information: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, "trapping" the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hair is used to document long-term (6 months-1 year) exposure.

Useful For: Detection of nonacute arsenic exposure in hair specimens

Interpretation: Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc. Hair arsenic levels above 1.00 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death.

Reference Values:
0-15 years: not established
> or =16 years: <1.0 mcg/g of hair


Arseonic, Nails

Clinical Information: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mees' lines, may appear in the fingernails.

Useful For: Detection of nonacute arsenic exposure

Interpretation: Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. Nail arsenic above 1.0 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death.

Reference Values:
0-15 years: not established
> or =16 years: <1.0 mcg/g of nails

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**Arsenic/Creatinine Ratio, Urine**

**Clinical Information:** Arsenic is a naturally occurring element that is widely distributed in the Earth’s crust. Arsenic is classified chemically as a metalloid, having properties of both a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As\(^{3+}\)/As\(^{III}\)) and arsenate (As\(^{5+}\)/As\(^{V}\)). Inorganic As\(^{V}\) is readily reduced to inorganic As\(^{III}\), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

**Useful For:** Screening for arsenic exposure using random urine specimens

**Interpretation:** Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated forms) or the relatively nontoxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As\(^{III}\) and As\(^{V}\)) are found in the urine shortly after ingestion, whereas the less toxic methylated forms monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As\(^{III}\) and As\(^{V}\) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.
Reference Values:
Only orderable as part of profile. For more information see:
- ASUCR / Arsenic/Creatinine Ratio, with Reflex, Random, Urine
- HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

Clinical References:

**ARSC**

**Arsenic/Creatinine Ratio, Urine**

Clinical Information: Arsenic is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenuocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As3+/AsIII) and arsenate (As5+/AsV). Inorganic AsV is readily reduced to inorganic As(III) which is then primarily broken down to less toxic methylated metabolites monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA).

In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and if not disposed of properly may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.
Useful For: Screening test for detection of arsenic exposure using random urine specimens

Interpretation: Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs methylated vs organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated forms) or the relatively non-toxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, AsIII and AsV) are found in the urine shortly after ingestion, whereas the less toxic methylated forms (MMA and DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary AsIII and AsV concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if you have been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in your body will affect your health.

Reference Values:
Only orderable as part of profile. For more information see:
  ARSCR / Arsenic/Creatinine, with Reflex, Random, Urine
  HMCRU / Heavy Metal/Creatinine, with Reflex, Random, Urine


ASUCR 608905

Arsenic/Creatinine, Ratio, with Reflex, Random, Urine

Clinical Information: Arsenic is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having properties of both a metal and a nonmetal. Elemental arsenic is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenite (DSMA), and monosodium methylarsenite (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are also added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles.
Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

**Useful For:** Preferred screening test for detection of arsenic exposure using random urine specimens

**Interpretation:** Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated forms) or the relatively nontoxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

**Reference Values:**

- 0-17 years: not established
- > or =18 years: <24 mcg/g creatinine

**Clinical References:**

Artichoke (Cynara scolymus) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35

Arylsulfatase A, 24 Hour, Urine

**Clinical Information:** Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and to a lesser extent, in visceral organs including the kidney and gallbladder. Cells that produce myelin are especially affected causing the characteristic leukodystrophy seen in MLD. Patients with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents before 30 months of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs and, unless successfully treated, most patients do not survive past childhood. Juvenile MLD (20%-30% of cases) is characterized by onset between 30 months to 16 years. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by variants in the ARSA gene coding for the ARSA enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however, the ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of arylsulfatase A, however, other sulfatase enzymes will also be deficient. Individuals with "pseudodeficiency" of ARSA have very low levels of ARSA activity, but are otherwise healthy. Pseudodeficiency is being recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population, therefore a diagnosis of MLD cannot be based upon reduced ARSA activity alone. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis, Varies), urinary excretion of sulfatides (CTSA / Ceramide Trihexosides and Sulfatides, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures, decline in mobility and cognitive ability, and feeding difficulties. Hematopoietic stem cell transplantation (HSCT) is an option but outcomes are dependent on the clinical stage and the presence of neurologic symptoms.

**Useful For:** Detection of arylsulfatase A deficiency using urine specimens This test is not suitable for carrier detection.

**Interpretation:** Reduced levels of arylsulfatase A are seen in patients with metachromatic leukodystrophy (MLD). Individuals with pseudodeficiency of arylsulfatase A can have results in the affected range, but are otherwise unaffected with MLD. Abnormal results should be confirmed using CTSA / Ceramide Trihexosides and Sulfatides, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis, Varies.

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
> or =19 nmol/h/mL

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels.

**Clinical References:**

**ARSAW**

**Arylsulfatase A, Leukocytes**

**Clinical Information:** Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and to a lesser extent, in visceral organs including the kidney and gallbladder. Cells that produce myelin are especially affected causing the characteristic leukodystrophy seen in MLD. Patients with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents before 30 months of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs and unless successfully treated, most patients do not survive past childhood. Juvenile MLD (20%-30% of cases) is characterized by onset between 30 months to 16 years old. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by variants in the ARSA gene coding for the ARSA enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however, the ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of arylsulfatase A, however, other sulfatase enzymes will also be deficient. Individuals with "pseudodeficiency" of ARSA have very low levels of ARSA activity but are otherwise healthy. Pseudodeficiency is being recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population, therefore a diagnosis of MLD cannot be based upon reduced ARSA activity alone. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis, Varies), urinary excretion of sulfatides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures, decline in mobility and cognitive ability, and feeding difficulties. Hematopoietic stem cell transplantation (HSCT) is an option but outcomes are dependent on the clinical stage and the presence of neurologic symptoms.

**Useful For:** Preferred enzymatic test for detection of arylsulfatase A deficiency This test is not suitable for carrier detection.
**Interpretation:** Reduced levels of arylsulfatase A are seen in patients with metachromatic leukodystrophy (MLD). Individuals with pseudodeficiency of arylsulfatase A can have results in the affected range but are otherwise unaffected with MLD. Abnormal results should be confirmed using CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis, Varies.

**Reference Values:**
> or = 62 nmol/h/mg

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels. Low normal values may be due to the presence of pseudodeficiency gene variant or carrier gene variant. Patients with these depressed levels may be phenotypically normal.

**Clinical References:**

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**Ascaris, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Ascaris worms Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>Level</td>
<td>Interpretation</td>
<td></td>
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<tr>
<td>------------</td>
<td>---------------------------------</td>
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</tr>
<tr>
<td>17.5-49.9</td>
<td>Strongly positive</td>
<td></td>
</tr>
<tr>
<td>50.0-99.9</td>
<td>Strongly positive</td>
<td></td>
</tr>
<tr>
<td>&gt;or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
<td></td>
</tr>
</tbody>
</table>


**VITC 42362 Ascorbic Acid (Vitamin C), Plasma**

**Clinical Information:** Vitamin C, also known as L-ascorbic acid or simply ascorbic acid, is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is an essential dietary component. Vitamin C is required for the enzymatic amidation of neuropeptides, production of adrenal cortical steroid hormones, promotion of the conversion of tropocollagen to collagen, and metabolism of tyrosine and folate. It also plays a role in lipid and vitamin metabolism and is a powerful reducing agent or antioxidant. Specific actions include: activation of detoxifying enzymes in the liver, antioxidation, interception and destruction of free radicals, preservation and restoration of the antioxidant potential of vitamin E, and blockage of the formation of carcinogenic nitrosamines. In addition, vitamin C appears to function in a variety of other metabolic processes in which its role has not been well characterized. Prolonged deficiency of vitamin C leads to the development of scurvy, a disease characterized by an inability to form adequate intercellular substance in connective tissues. This results in the formation of swollen, ulcerative lesions in the gums, mouth, and other tissues that are structurally weakened. Early symptoms may include weakness, easy fatigue and listlessness, as well as shortness of breath, and aching joints, bones, and muscles. The need for vitamin C can be increased by the use of aspirin, oral contraceptives, tetracycline, and a variety of other medications. Psychological stress and advancing age also tend to increase the need for vitamin C. Among the elderly, lack of fresh fruit and vegetables often adds vitamin C depletion to the inherently increased need, with development of near-scurvy status.

**Useful For:** Diagnosing vitamin C deficiency As an aid to deter excessive intake

**Interpretation:** Values below 0.2 mg/dL indicate significant deficiency. Values greater than or equal to 0.2 mg/dL and less than 0.4 mg/dL are consistent with a moderate risk of deficiency due to inadequate tissue stores. Values of 0.4 to 2.0 mg/dL indicate adequate supply. The actual level at which vitamin C is excessive has not been defined. Values above 3.0 mg/dL are suggestive of excess intake. Whether vitamin C in excess is indeed toxic continues to be uncertain. However, limited observations suggest that this condition may induce uricosuria and, in individuals with glucose-6-phosphate dehydrogenase deficiency, may induce increased red blood cell fragility.

**Reference Values:**
0.4-2.0 mg/dL

**Clinical References:**
**Clinical Information:** Certain genetic diseases are more common in individuals of Ashkenazi Jewish heritage (Jewish individuals of Eastern European ancestry) compared to the non-Jewish population. The majority of these conditions are inherited in an autosomal recessive manner. This group of diseases includes Gaucher, Tay-Sachs, familial dysautonomia, Canavan, mucolipidosis IV, Niemann-Pick Type A and B, FANCC-related Fanconi anemia, and Bloom syndrome. While these conditions are observed outside of the Ashkenazi Jewish population, they occur at a lower frequency. It is estimated that an individual of Ashkenazi Jewish ancestry has a 20% to 25% chance of being a carrier of 1 of these diseases. Gaucher Disease: Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Mutations in the beta-glucocerebrosidase gene, GBA, cause the clinical manifestations of Gaucher disease. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. Type 1 disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. There is a broad spectrum of disease in type 1, with some patients exhibiting severe symptoms and others very mild disease. Types 2 and 3 are associated with neurological disease of variable onset and progression, though type 2 tends to be more severe. Eight common GBA mutations, including the N370S mutation most commonly found in the Ashkenazi Jewish population, are included in this test: deltaA55bp, V394L, N370S, IVS2+1G>A, 84G>GG, R496H, L444P, and D409H. Tay-Sachs: Tay-Sachs disease is caused by an absence of hexosaminidase (HexA) enzyme activity, which results in the accumulation of the sphingolipid GM2 ganglioside. Mutations in the HEXA gene cause the clinical manifestations of Tay-Sachs disease (TSD). The most common form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations of this condition include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. This panel tests for the 3 common mutations in the Ashkenazi Jewish population: 1278insTATC, G269S, and IVS12+1G>C. Also included in this assay are the mutations IVS9+1G>A and delta7.6kb mutations along with the R247W and R249W polymorphisms associated with pseudodeficiency. Familial Dysautonomia: Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons. Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal degeneration continues throughout the lifespan. Mutations in the IKBKAP gene cause the clinical manifestations of familial dysautonomia. Two mutations in the IKBKAP gene are common in the Ashkenazi Jewish population: IVS20(+6)T>C and R696P. Canavan Disease: Canavan disease is a severe leukodystrophy resulting from a deficiency of the enzyme aspartoacylase. Mutations in the ASPA gene cause the clinical manifestations of Canavan disease. The deficiency of aspartoacylase leads to spongy degeneration of the brain, and the disease is characterized by delayed development beginning at age 3 to 6 months, head lag, macrocephaly, and hypotonia. Death usually occurs in the first decade of life. Four ASPA mutations are included in this test: 433(2-1)A>G, A305E, E285A, and Y231X. Mucolipidosis IV: Mucolipidosis IV is a lysosomal storage disease characterized by mental retardation, hypotonia, corneal clouding, and retinal degeneration. Mutations in the MCOLN1 gene are responsible for the clinical manifestations of mucolipidosis IV. Two mutations in the MCOLN1 gene account for the majority of mutations in the Ashkenazi Jewish population: IVS3(-2)A>G and delta6.4kb. Niemann-Pick Disease Types A and B: Niemann-Pick disease (types A and B) is a lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is milder, though variable in its clinical presentation. Most individuals with type B do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are known to cause Niemann-Pick disease types A and B. There are 3 common mutations causing Niemann-Pick type A in the Ashkenazi Jewish population: L302P, R496L, and fsP330. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutation alleles in Gran Canaria Island. Fanconi Anemia: Fanconi anemia is an aplastic anemia that leads to bone marrow failure and myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, IVS4(+4)A>T, in the FANCC gene is common in the Ashkenazi Jewish population. A second mutation, 322delG, is over represented in FANCC patients of Northern European ancestry. Bloom
Syndrome: Bloom syndrome is characterized by short stature, sun sensitivity, susceptibility to infections, and a predisposition to cancer. Mutations in the BLM gene lead to genetic instability (increased chromosomal breakage and sister chromatid exchange) and cause the clinical manifestations of Bloom syndrome. The protein encoded by the BLM gene is a helicase involved in maintaining DNA integrity. There is a common mutation in the Ashkenazi Jewish population:

2281delATCTGAinsTAGATTC (2281del6/ins7). Because of the high sensitivity of carrier testing in the Ashkenazi Jewish population, the American College of Medical Genetics and Genomics (ACMG) recommends that carrier screening for cystic fibrosis (CF), Canavan, Tay-Sachs, familial dysautonomia, Niemann-Pick type A, Fanconi anemia (FANCC), Bloom syndrome, mucolipidosis IV, and Gaucher disease be offered to individuals of Ashkenazi Jewish ancestry. The mutation detection rates and carrier frequencies for the diseases included in this panel are listed below. Of note, testing for CF is not included in this panel. If testing for this disorder is desired, please see details and ordering information under CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel. Disease Carrier Rate in the AJ Population Mutation Detection Rate Gaucher 1/18 95% Tay-Sachs 1/31 *99% Familial dysautonomia 1/31 99% Canavan 1/41 98% Mucolipidosis IV 1/127 95% Niemann-Pick type A/B 1/90 97%

FANCC-related Fanconi anemia 1/89 >99% Bloom syndrome 1/107 >99% *with biochemical testing

The Ashkenazi Jewish panel is useful for identifying carriers of these 8 conditions in an at-risk population. Because the diseases included in the panel are inherited in an autosomal recessive manner, the presence of a family history is not a prerequisite for testing consideration. The identification of disease-causing mutations allows for carrier testing of at-risk family members and prenatal diagnosis for pregnancies in which both parents are known carriers. Refer to Carrier Testing for Tay-Sachs Disease and Other GM2 Gangliosidosis Variants: Supplementing Traditional Biochemical Testing with Molecular Methods, Mayo Medical Laboratories Communique 2004 Jul;29(7) for more information regarding diagnostic strategy. Of note, approximately 1 in 25 individuals of Ashkenazi Jewish ancestry are also carriers of cystic fibrosis (CF). Therefore, the American College of Medical Genetics also recommends that carrier screening for CF be offered to individuals of Ashkenazi Jewish ancestry who are pregnant or considering pregnancy. Carrier screening for CF is available by ordering CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel.

Useful For: Carrier screening in individuals of Ashkenazi Jewish ancestry for Bloom syndrome, Canavan disease, FANCC-related Fanconi anemia, familial dysautonomia, Gaucher disease, mucolipidosis IV, Niemann-Pick disease types A and B, and Tay-Sachs disease

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.


Asparagin, IgE, Serum

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

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

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

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
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<tr>
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</tr>
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Reference values apply to all ages.


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**Aspartate Aminotransferase (AST) (GOT), Serum**

**Clinical Information:** Aspartate aminotransferase (AST) is found in high concentrations in liver, heart, skeletal muscle, and kidney. AST is present in both cytoplasm and mitochondria of cells. In cases involving mild tissue injury, the predominant form of AST is that from the cytoplasm. Severe tissue damage results in more of the mitochondrial enzyme being released. High levels of AST can be found in cases such as myocardial infarction, acute liver cell damage, viral hepatitis, and carbon tetrachloride poisoning. Slight to moderate elevation of AST is seen in muscular dystrophy, dermatomyositis, acute pancreatitis, and crushed muscle injuries.

**Useful For:** Diagnosing and monitoring liver disease, particularly diseases resulting in a destruction of hepatocytes

**Interpretation:** Elevated aspartate aminotransferase (AST) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the normal range. Levels may reach values as high as 100 times the upper reference limit, although 20- to 50-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions affecting the liver, alanine aminotransferase (ALT) is characteristically as high as or higher than AST, and the ALT:AST ratio, which normally and in other condition is less than 1, becomes greater than unity. AST levels are usually elevated before clinical signs and symptoms of disease appear. Five- to 10-fold elevations of both AST and ALT occur in patients with primary or metastatic carcinoma of the liver, with AST usually being higher than ALT, but levels are often normal in the early stages of malignant infiltration of the liver. Elevations of ALT activity persist longer than do those of AST activity. Elevated AST values may also be seen in disorders affecting the heart, skeletal muscle, and kidney.

**Reference Values:**

Males
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L


FASPE
57947

Aspen (Populus tremuloides) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

ASPAG
84356

Aspergillus (Galactomannan) Antigen, Serum

Clinical Information: Invasive aspergillosis (IA) is a severe infection that occurs in patients with prolonged neutropenia, following transplantation or in conjunction with aggressive immunosuppressive regimens (eg, prolonged corticosteroid usage, chemotherapy). The incidence of IA is reported to vary from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to 80% due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death).

Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA requires histopathological evidence of deep-tissue invasion or a positive culture. However, this evidence is often difficult to obtain due to the critically ill nature of the patient and the fact that severe thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The sensitivity of culture in this setting also is low, reportedly ranging from 30% to 60% for bronchoalveolar lavage fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography: CT scan); definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the FDA for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of galactomannan can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs.

Useful For: Aiding in the diagnosis of invasive aspergillosis Assessing response to therapy

Interpretation: A positive result supports a diagnosis of invasive aspergillosis (IA). Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence. See Cautions. A negative result does not rule out the diagnosis of IA. Repeat testing is recommended if the result is negative but IA is suspected. Patients at risk of IA should have a baseline serum tested and should be monitored twice a week for increasing galactomannan antigen levels. Galactomannan antigen levels may be useful in the assessment of therapeutic response. Antigen levels decline in response to antimicrobial therapy.

Reference Values:
<0.5 index
Reference values apply to all ages.

Clinical References: 1. Maertens J, Verhaegen J, Lagrou K, Boogaerts M: Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic
patients and stem cell transplantation recipients: a prospective evaluation. Blood. 2001 March
fumigatus galactomannan: value and limits of the Platelia test for diagnosing invasive aspergillosis. J Clin
Specificity of a sandwich enzyme-linked immunosorbent assay for detecting Aspergillus galactomannan.
Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of
Infectious Diseases. 9th ed. Elsevier; 2020:3103-3116

FASAB 75571
Aspergillus Antibodies, Quantitative, DID
Reference Values:
Aspergillus fumigatus Â Neg: <1:1
Aspergillus flavus Â Neg: <1:1
Aspergillus niger Â Neg: <1:1

ASPBA 61009
Aspergillus Antigen, Bronchoalveolar Lavage
Clinical Information: Invasive aspergillosis (IA) is a severe infection that occurs in patients with
prolonged neutropenia following transplantation or in conjunction with aggressive immunosuppressive
regimens (eg, prolonged corticosteroid use, chemotherapy). The incidence of IA is reported to vary
from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to
80%, due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death).
Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA
requires histopathological evidence of deep-tissue invasion or a positive culture. However, this evidence
is often difficult to obtain due to the critically ill nature of the patient and the fact that severe
thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The
sensitivity of culture in this setting also is low, reportedly ranging from 30% to 60% for
bronchoalveolar lavage (BAL) fluid. Accordingly, the diagnosis is often based on nonspecific clinical
symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence
(computed tomography scan), and a definitive diagnosis is often not established before fungal
proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was
approved by the FDA for the detection of galactomannan, a molecule found in the cell wall of
Aspergillus species. Serum galactomannan (Aspergillus antigen) can often be detected a mean of 7 to 14
days before other diagnostic clues become apparent, and monitoring of Aspergillus antigen can
potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs.
The clinical utility of Aspergillus antigen testing in BAL specimens as an early prognostic indicator of
IA has recently been assessed. These studies demonstrated equivalent or higher sensitivity compared to
detection of Aspergillus antigen in serum. (1-4) This assay may be useful in the assessment of
therapeutic response as antigen levels typically decline in response to effective antimicrobial therapy.

Useful For: Aiding in the diagnosis of invasive aspergillosis and assessing response to therapy

Interpretation: A positive result in bronchoalveolar lavage (BAL) fluid supports a diagnosis of
invasive, pulmonary aspergillosis. Positive results should be considered in conjunction with other
diagnostic procedures, such as microbiologic culture, histologic examination of biopsy specimens, and
radiographic evidence (see Cautions). A negative result in BAL fluid does not rule out the diagnosis of
invasive aspergillosis (IA). Patients at risk of IA should be monitored twice a week for Aspergillus
antigen levels in serum until determined to be clinically unnecessary. Aspergillus antigen levels
typically decline in response to effective antimicrobial therapy.

Reference Values:
<0.5 Index

FAFE
57910

Aspergillus flavus IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 ÅEæ,¬ÅÊœ 0.69 Low Positive 2 0.70 ÅEæ,¬ÅÊœ 3.49 Moderate Positive 3 3.50 ÅEæ,¬ÅÊœ 17.49 Positive 4 17.50 ÅEæ,¬ÅÊœ 49.99 Strong Positive 5 50.00 ÅEæ,¬ÅÊœ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

ASP
82911

Aspergillus fumigatus, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to Aspergillus fumigatus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<tr>
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<tr>
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<tr>
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</table>
Aspergillus fumigatus, IgG Antibodies, Serum

**Clinical Information:** Aspergillus fumigatus is one of the causative agents of hypersensitivity pneumonitis (HP), as well as invasive lung disease with cavititation or pneumonitis and allergic bronchopulmonary disease. Other causative microorganisms of HP include Micropolyspora faeni and Thermoactinomyces vulgaris. The development of HP and allergic bronchopulmonary disease caused by Aspergillus fumigatus is accompanied by an immune response to Aspergillus fumigatus antigens with production of IgG or IgE antibodies, respectively. While the immunopathogenesis of HP and allergic bronchopulmonary disease is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.

**Useful For:** Evaluation of patients suspected of having lung disease caused by Aspergillus fumigatus

**Interpretation:** Elevated concentrations of IgG antibodies to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**
- <4 years: not established
- > or =4 years: < or =102 mg/L

**Clinical References:**

Aspergillus IgG Precipitins Panel

**Interpretation:** The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

**Reference Values:**
- Negative

Aspergillus niger, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to Aspergillus niger Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**ADMA 607697**

**Asymmetric Dimethylarginine, Plasma**

**Clinical Information:** Asymmetric dimethylarginine (ADMA) is an independent risk factor for major adverse cardiovascular events.(1-7) ADMA inhibits nitric oxide (NO) synthesis and is elevated in diseases related to endothelial dysfunction including hypertension, hyperlipidemia, and type II diabetes mellitus. Elevation in ADMA and subsequent NO synthesis inhibition leads to vasoconstriction, reduced peripheral blood flow, and reduced cardiac output. Elevated plasma ADMA confers a 4- to 6-fold increased risk of subsequent cardiovascular events or mortality among patients with acute coronary syndrome,(3) unstable angina,(4) type II diabetes mellitus,(5) end-stage renal disease,(6) coronary heart disease,(7) and peripheral artery disease.(1) Baseline ADMA remained a significant risk factor of adverse events even after adjusting for low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, creatinine, and high-sensitivity C-reactive protein. Plasma ADMA concentrations are lowered by rosuvastatin and atorvastatin, but not simvastatin in patients with hypercholesterolemia.(8) Addition of vildagliptin (Galvus) to metformin significantly reduced ADMA concentrations among patients with type II diabetes mellitus.(9)

**Useful For:** Assessing the likelihood of future coronary events in patients with coronary heart disease, type II diabetes mellitus, or kidney disease Prompting intervention and assessing improvements among subjects with elevated ADMA and hypercholesterolemia or type II diabetes mellitus

**Interpretation:** In patients with preexisting coronary conditions or at high risk for coronary events
(diabetes, renal insufficiency), asymmetric dimethylarginine (ADMA) levels in the upper tertile, above 112 ng/mL, confer an increased risk for future coronary events.

**Reference Values:**
> or =18 years: 63-137 ng/mL  
Reference values have not been established for patients who are <18 years of age

**Clinical References:**

**ATRX Immunostain, Technical Component Only**

**Clinical Information:** This test is intended to identify the presence of ATP-dependent helicase ATRX, X-linked helicase II (ATRX) protein. ATRX is produced by most mitotically active normal cells and can be useful in the distinction of differentiated from undifferentiated neoplasms.

**Useful For:** Distinguishing differentiated from undifferentiated neoplasms

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Atypical Hemolytic Uremic Syndrome (aHUS) Complement Panel, Serum and Plasma

Clinical Information: Individuals presenting with thrombotic microangiopathies (TMA) require clinical testing to identify the underlying cause. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are both acute syndromes with many overlapping clinical features. Reduced levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motives, member 13) activity is associated with TTP and is one laboratory feature that distinguishes TTP from HUS. HUS can also have a number of causes; one of the rarer forms of disease is caused by defects in the alternative pathway of the complement system, so called atypical-HUS (aHUS). Patients with defective alternative pathway regulation can benefit from biologics that suppress the complement system. The purpose of this panel is to aid in the differential diagnosis of TMA. The suggested approach is to rule-out other causes of TMA first, since aHUS is one of the rarer causes of TMA. Additionally, the assays can be used in the setting of membranoproliferative glomerulonephritis (MPGN) and can help distinguish between immune-complex mediated or complement-mediated kidney disease. MPGN mediated by immune-complexes are ones resulting from infectious processes, autoimmune diseases, or monoclonal gammopathies; whereas complement-mediated MPGN can be subdivided in C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), based on electron microscopy of the kidney biopsy histological findings. Despite phenotypic differences, these glomerular diseases share dysfunction of the alternative pathway as the defining pathophysiology.

Useful For: Detecting deficiencies in the alternative pathway that can cause atypical-hemolytic uremic syndrome, dense deposit disease, and C3 glomerulonephritis A second-tier test that aids in the differential diagnosis of thrombotic microangiopathies

Interpretation: An interpretive report will be included.

Reference Values:
FACTOR B COMPLEMENT ANTIGEN
15.2-42.3 mg/dL

SC5b-9 COMPLEMENT
< or =250 ng/mL

FACTOR H COMPLEMENT ANTIGEN
18.5 to 40.8 mg/dL

C4d COMPLEMENT ACTIVATION FRAGMENT
< or =9.8 mcg/mL

CBb COMPLEMENT ACTIVATION FRAGMENT
< or =1.6 mcg/mL

COMPLEMENT C4
14-40 mg/dL

COMPLEMENT C3
75-175 mg/dL

ALTERNATIVE COMPLEMENT, PATHWAY (AH50) FUNCTIONAL> or =46% normal

COMPLEMENT, TOTAL
30-75 U/mL


**AudioloGene Hereditary Hearing Loss Panel, Varies**

**Clinical Information:** Hereditary hearing loss encompasses a heterogeneous group of syndromic and nonsyndromic conditions. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for hearing loss and, therefore, identify other organ systems that may be involved, establish long-term prognosis, and ascertain the inheritance pattern and recurrence risk within a family. Individuals with syndromic hearing loss typically have involvement of other organs or organ systems and may have malformations of the external ear. Individuals with nonsyndromic hearing loss may have abnormalities of the middle ear and/or inner ear but typically do not have visible abnormalities of the external ear and often do not have additional organ system involvement or other related medical problems. Approximately 50% of individuals with hearing loss have a genetic etiology that can be identified. Of those, approximately 70% of individuals have a nonsyndromic condition, and the remaining 30% have 1 of over 400 syndromes involving hearing loss. Of the individuals with nonsyndromic hearing loss, at least three-quarters have an autosomal recessive condition, approximately 25% of whom have variants in the GJB2 or GJB6 genes.

**Useful For:** Establishing a diagnosis of a syndromic or nonsyndromic hereditary hearing loss disorder Identifying variants within genes known to be associated with hereditary hearing loss, allowing for predictive testing of at-risk family members

**Interpretation:** Variant curation is performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**Aureobasidium pullulans, IgE, Serum**

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

Useful For: Establishing a diagnosis of an allergy to Aureobasidium pullulans Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>6</td>
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</tr>
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Reference values apply to all ages.


Australian Pine, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to the Australian pine Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**Autoimmune Axonal Evaluation, Serum**

**Clinical Information:** Neuropathy patients have variable sensory disturbance (loss or exaggerated sensation) with pain, weakness, and autonomic involvements such as sweat abnormalities, gastrointestinal dysfunction, and lightheadedness on standing. These symptoms are as a result of injury to the distal nerves, roots, ganglia or their gathering points (nerve plexus in the thighs and arms). Patients may have symmetric or asymmetric involvements of the extremities, trunk, and head including extraocular muscles. Subacute onsets and asymmetric involvements favor inflammatory or immune causes over inherited or metabolic forms. Depending on the specific inflammatory or immune mediated causes other parts of the nervous system may also be affected (brain, cerebellum, spinal cord). In the evaluation of patients with immune mediated autoantibody neuropathies, nerve conduction studies and needle electromyography can help to classify the neuropathy as either: 1) primary axonal; 2) primary demyelinating; or 3) mixed axonal and demyelinating. This evaluation focuses on persons with primary axonal forms. Well established neuronal autoantibodies responsible for axonal neuropathies include: antineuronal nuclear antibodies (ANNA1 and 3), Purkinje cytoplasmic antibody (PCA1 and 2), amphiphysin antibody, collapsin response mediator protein 5 (CRMP5) antibody, leucine-rich glioma inactivated 1 protein (LG11) antibody, and contactin-associated response protein 2 (CASPR2) antibody. Other autoantibodies have preliminary evidence to support their association with neuropathy including: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) antibody, antiglial nuclear antibody (AGNA); antineuronal nuclear type 2 antibody (ANNA2), gamma-aminobutyric acid B receptor (GABABR) antibody, glutamic acid decarboxylase 65 (GAD65) receptor antibody, glial fibrillary acidic protein (GFAP) antibody, N-methyl-D-aspartate receptor (NMDAR) antibody, Purkinje cell cytoplasmic Tr (PCA-Tr) antibody, dipeptidyl-peptidase-like protein-6 (DPPX) antibody, and metabotropic glutamate receptor 1 (mGluR1). A patient's humoral and cellular immune response leads to the neurological syndrome. This may be related to an underlying cancer or unidentified antigen trigger. If related to cancer it may be a new or recurrent malignancy, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons, glia, or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. Cancers recognized in this context most commonly are small-cell lung carcinoma, thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and...
chondroblastoma. This evaluation focuses on those antibodies with known associations with varied forms of peripheral axonal neuropathy. Seropositive patients usually present with subacute neurological symptoms of radiculopathy; plexopathy; or sensory, sensorimotor, or autonomic neuropathy, with or without a neuromuscular transmission disorder such as neuromuscular hyperexcitability. Other peripheral manifestation includes cranial neuropathies, especially loss of vision, hearing, smell, or taste. Commonly beyond the peripheral manifestation are encephalopathy, seizures, cerebellar ataxia, and myelopathy. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, and limbic encephalopathy. Cancer risk factors include past or family history of cancer, history of smoking, or social or environmental exposure to carcinogens.

**Useful For:** Evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer Directing a focused search for cancer Investigating neurological symptoms that appear in the course of, or after, cancer therapy, and are not explainable by metastasis Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy Detecting early evidence of cancer recurrence in previously seropositive patients

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. More than one paraneoplastic autoantibody may be detected and associated with specific cancers.

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Autoimmune Dysautonomia Evaluation, Serum

Clinical Information: Autoimmune dysautonomia encompasses disorders of peripheral autonomic synapses, ganglionic neurons, autonomic nerve fibers, and central autonomic pathways mediated by neural-specific IgG or effector T cells. These disorders may be idiopathic or paraneoplastic, subacute or insidious in onset, and may present as a limited disorder or generalized pandysautonomia. Pandysautonomia is usually subacute in onset and severity and includes impaired pupillary light reflex, anhidrosis, orthostatic hypotension, cardiac arrhythmias, gastrointestinal dysmotility, sicca manifestations, and bladder dysfunction. Limited dysautonomia is confined to one or just a few domains, is often mild, and may include sicca manifestations, postural orthostatism and cardiac arrhythmias, bladder dysfunction, or gastrointestinal dysmotilities. Diagnosis of limited dysautonomia requires documentation of objective abnormalities by autonomic reflex testing, thermoregulatory sweat test, or gastrointestinal motility studies. The most commonly encountered autoantibody marker of autoimmune dysautonomia is the neuronal ganglionic alpha-3-acetylcholine receptor (AChR) autoantibody. This autoantibody to date is the only proven effector of autoimmune dysautonomia. A direct relationship has been demonstrated between antibody titer and severity of dysautonomia in both alpha-3-AChR-immunized animals and patients with autoimmune dysautonomia. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally have profound pandysautonomia. Dysautonomic patients with lower alpha-3-AChR autoantibody values (0.03-0.99 nmol/L) have limited dysautonomia. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancers recognized most commonly include small-cell lung carcinomas, thymoma, adenocarcinomas of breast, lung, prostate, and gastrointestinal tract, and lymphoma. Cancer risk factors include a past or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors neurologic improvement and lessens morbidity. Autoantibodies to other onconeural proteins shared by neurons, glia or muscle (eg, antineuronal nuclear autoantibody-type 1: ANNA-1, CRMP-5-IgG) serve as additional markers of paraneoplastic or idiopathic dysautonomia. A specific neoplasm is often predictable by the individual patient's autoantibody profile.

Useful For: Investigating idiopathic dysautonomic symptoms Directing a focused search for cancer in patients with idiopathic dysautonomia Investigating autonomic symptoms that appear in the course or wake of cancer therapy and are not explainable by recurrent cancer or metastasis (detection of autoantibodies in this profile helps differentiate autoimmune dysautonomia from the effects of chemotherapy)

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscle, and glia are valuable serological markers of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than one autoantibody to be detected in patients with autoimmune dysautonomia. These include: -Plasma membrane cation channel antibodies (neuronal ganglionic [alpha-3]). All of these autoantibodies are potential effectors of autonomic dysfunction. -Antineuronal nuclear autoantibody-type 1 -Neuronal and muscle cytoplasmic antibodies (CRMP-5 IgG) A rising autoantibody titer in previously seropositive patients suggests cancer recurrence.

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*Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, CRMP-5-IgG, PCA-1, PCA-2, or PCA-Tr may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable." Note: CRMP-5 titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 800-533-1710 to request CRMP-5 Western blot.

**Clinical References:**
Autoimmune Gastrointestinal Dysmotility Evaluation, Serum

**Clinical Information:** Autoimmune gastrointestinal dysmotility (AGID) is a limited form of dysautonomia (also known as autoimmune autonomic ganglionopathy or neuropathy) that is sometimes a paraneoplastic disorder. Neoplasms most commonly found are lung cancer, thymoma, and miscellaneous adenocarcinomas. Diagnosis is confirmed by objective abnormalities on gastrointestinal (GI) motility studies (eg, gastric, small intestinal or colonic nuclear transit studies; esophageal, gastroduodenal, or colonic manometry or anorectal manometry with balloon expulsion). These disorders target autonomic postganglionic synaptic membranes and in some cases ganglionic neurons and autonomic nerve fibers, and may be accompanied by sensory small fiber neuropathy. Onset may be subacute or insidious. There may be additional manifestations of dysautonomia (eg, impaired pupillary light reflex, anhidrosis, orthostatic hypotension, sicca manifestations, and bladder dysfunction) or signs of other neurologic impairment. Autonomic reflex testing and a thermoregulatory sweat test are valuable aids in documentation of objective abnormalities. The serological profile of AGID may include autoantibodies specific for onconeural proteins found in the nucleus, cytoplasm, or plasma membrane of neurons or muscle. Some of these autoantibodies are highly predictive of an underlying cancer. A commonly encountered autoantibody marker of AGID is the ganglionic neuronal alpha-3- acetylcholine receptor (alpha-3-AChR) autoantibody. The pathogenicity of this autoantibody was demonstrated in rabbits immunized with a recombinant extracellular fragment of the alpha-3-AChR subunit, and in mice injected with IgG from high-titered alpha-3-AChR autoantibody-positive rabbit or human sera. A direct relationship between antibody titer and severity of dysautonomia occurs in both experimental animals and patients. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally present with profound pandysautonomia, and those with lower alpha-3-AChR autoantibody values may have limited autoimmune dysautonomia or other neurological signs and symptoms. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancer risk factors include the patient’s past or family history of cancer, history of smoking, or social and environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors less morbidity from the GI dysmotility disorder. The cancers recognized most commonly with alpha-3-AChR autoantibody include adenocarcinomas of breast, lung, prostate, and GI tract, or lymphoma. A specific neoplasm is often predictable when a patient’s autoantibody profile includes other autoantibodies to onconeural proteins shared by neurons, glia, or muscle. Small-cell lung carcinoma is found in 80% of antineuronal nuclear antibody-type 1 (ANNA-1; anti-Hu)-positive patients and 23% of ANNA-1-positive patients have GI dysmotility. The most common GI manifestation is gastroparesis, but the most dramatic is pseudoobstruction.

**Useful For:** Investigating unexplained weight loss, early satiety, anorexia, nausea, vomiting, constipation or diarrhea in a patient with past or family history of cancer or autoimmunity Directing a focused search for cancer Investigating gastrointestinal symptoms that appear in the course or wake of cancer therapy, not explainable by recurrent cancer, metastasis or therapy; detection of autoantibodies on this profile helps differentiate autoimmune gastrointestinal dysmotility from the effects of chemotherapy Detecting early evidence of cancer recurrence in previously seropositive patients who have a rising titer of 1 or more autoantibodies

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient’s immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute symptoms and signs. It is not uncommon for more than one antibody to be detected. Three classes of antibodies are recognized (the individual antibodies from each class included in the profile are denoted in parentheses): -Antineuronal nuclear autoantibody-type 1 -Neuronal and muscle cytoplasmic (collapsin response-mediator protein-5) -Plasma membrane cation channel (neuronal ganglionic alpha-3-acetylcholine receptor). All of these autoantibodies are potential effectors of autoimmune gastrointestinal dysmotility.

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PCATR  Purkinje Cell Cytoplasmic AbIFA  Type Tr

Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, PCA-1, PCA-2, or PCA-Tr may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable." CRMP-5 titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 1-800-533-1710 to request CRMP-5 Western blot.

Clinical References:

Autoimmune Liver Disease Panel, Serum

Clinical Information: Autoimmune liver diseases result from damage to hepatocytes or cholangiocytes caused by an inflammatory immune reaction. Included within this disease group are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). In some cases, patients with these diseases may present asymptomatically, with increases in various liver enzymes being identified incidentally during an unrelated clinical evaluation. On the other end of the spectrum are patients who present with clinical evidence of liver disease, including fatigue, hepatomegaly, ascites, esophageal varices, and jaundice. Diagnosis of an autoimmune liver disease first requires that other etiologies of liver injury, including viral, drug, and metabolic causes, be excluded. In some situations, a liver biopsy may be indicated. For those patients in whom an autoimmune liver disease is suspected, autoantibody serology testing may be considered. This assay includes markers that may support a diagnosis of an autoimmune liver disease, specifically AIH or PBC. Unfortunately, there are no known autoantibodies specific for PSC that are useful as diagnostic markers. Patients with AIH may be positive for smooth muscle antibodies (SMA) and/or antinuclear antibodies (ANA). The SMA associated with AIH are generally specific for F-actin. SMA have a specificity of 80% to 90% for AIH, although the sensitivity is only in the range of 70% to 80%. In contrast, ANA, although relatively sensitive for AIH, lack specificity, being associated with a variety of autoimmune diseases. Both SMA and ANA, along with other lab markers and biopsy evaluation, are included in the international diagnostic criteria for AIH. Antimitochondrial antibodies (AMA) are a diagnostic marker for PBC. AMA are found in more than 90% of patients with PBC, with a specificity of greater than 95%. AMA are included in the diagnostic criteria.
for PBC, which were developed through an international collaborative effort.

**Useful For:** Evaluation of patients with suspected autoimmune liver disease, specifically autoimmune hepatitis or primary biliary cirrhosis. Evaluation of patients with liver disease of unknown etiology.

**Interpretation:** The presence of smooth muscle antibodies (SMA) or antinuclear antibodies (ANA) is consistent with a diagnosis of chronic autoimmune hepatitis, in patients with clinical or laboratory evidence of hepatocellular damage. The presence of antimitochondrial antibodies (AMA) is consistent with a diagnosis of primary biliary cirrhosis, in patients with clinical or laboratory evidence of hepatobiliary damage.

**Reference Values:**

**SMOOTH MUSCLE ANTIBODIES**
- Negative
- If positive, results are titered.
- Reference values apply to all ages.

**MITOCHONDRIAL ANTIBODIES (M2)**
- Negative: <0.1 Units
- Borderline: 0.1-0.3 Units
- Weakly positive: 0.4-0.9 Units
- Positive: > or =1.0 Units
- Reference values apply to all ages.

**ANTINUCLEAR ANTIBODIES (ANA2)**
- Negative: < or =1.0 Units
- Weakly positive: 1.1-2.9 Units
- Positive: 3.0-5.9 Units
- Strongly positive: > or =6.0 Units
- Reference values apply to all ages.


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**MAS1 605125 Autoimmune Myelopathy Evaluation, Serum**

**Clinical Information:** Patients with autoimmune myelopathy present with subacute onset and rapid progression of spinal cord symptoms with one or more of the following: weakness, gait difficulties, loss of sensation, neuropathic pain, and bowel and bladder dysfunction. Clinical history and examination, spinal cord magnetic resonance imaging, and cerebrospinal fluid (CSF) testing may provide clues to an autoimmune diagnosis. Autoimmune myelopathy evaluation of both serum and CSF can assist in the diagnosis (paraneoplastic or idiopathic autoimmune) and aid distinction from other causes of myelopathy (multiple sclerosis, sarcoidosis, vascular disease). Early testing may assist in early diagnosis of occult cancer, prompt initiation of immune therapies, or both.

**Useful For:** Evaluating patients with suspected autoimmune myelopathy, myelitis, paraneoplastic myelopathy using serum specimens.

**Interpretation:** A positive result is consistent with a diagnosis of autoimmune myelopathy in the appropriate clinical context.

**Reference Values:**

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Test ID | Reporting name | Methodology | Reference value |
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**MOGTS**  MOG FACS Titer, S  Flow cytometry

**NFHCS**  NIF Heavy Chain CBA, S  CBA  Negative

**NIFTS**  NIF IFA Titer, S  IFA

**NFLCS**  NIF Light Chain CBA, S  CBA  Negative

**NMDCS**  NMDA-R Ab CBA, S  CBA  Negative

**NMDIS**  NMDA-R Ab IF Titer Assay, IFA  S

**NMOTS**  NMO/AQP4 FACS Titer, S  Flow cytometry  Negative

**PC1BS**  PCA-1 Immunoblot, S  IB  Negative Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, CRMP-5-IgG, PCA-1, PCA-2, or PCA-Tr may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

**PCTBS**  PCA-Tr Immunoblot, S  IB

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**Clinical References:**

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**Autoimmune Myelopathy Evaluation, Spinal Fluid**

**Clinical Information:** Patients with autoimmune myelopathy present with subacute onset and rapid progression of spinal cord symptoms with one or more of the following: weakness, gait difficulties, loss of sensation, neuropathic pain, and bowel and bladder dysfunction. Clinical history and examination, spinal cord magnetic resonance imaging and cerebrospinal fluid (CSF) testing may provide clues to an autoimmune diagnosis. Autoimmune myelopathy evaluation of both serum and CSF can assist in the diagnosis (paraneoplastic or idiopathic autoimmune), and aid distinction from other causes of myelopathy (multiple sclerosis, sarcoidosis, vascular disease). Early testing may assist in early diagnosis of occult cancer, prompt initiation of immune therapies, or both.

**Useful For:** Evaluating patients with suspected autoimmune myelopathy, myelitis, paraneoplastic myelopathy using spinal fluid specimens

**Interpretation:** A positive result is consistent with a diagnosis of autoimmune myelopathy in the appropriate clinical context.

**Reference Values:**

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Clinical References:

**FARP 75446**

Autoimmune Retinopathy Panel by Immunoblot (ARP)

Reference Values:
A final report will be provided.

**AUTOP 65666**

Autoinflammatory Primary Immunodeficiency (PID) Gene Panel, Varies

Clinical Information: Autoinflammatory disorders include several monogenic defects associated with abnormal activation of the innate immune system leading to clinically evident inflammation and high levels of acute-phase reactants. These disorders typically present in childhood, often manifesting with unexplained fevers. While these features can mimic infections or hematological neoplasias, the inflammatory lesions are non-neoplastic and sterile. While periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) syndrome (aphthous stomatitis, pharyngitis, and adenitis), systemic juvenile idiopathic arthritis (sJIA), adult-onset Still disease, and Behcet disease overlap phenotypically with autoinflammatory conditions, a genetic cause of these disorders has not been identified and, therefore, they are not included on this panel. Several of the autoinflammatory conditions represented on this panel are responsive to IL-1 blocking therapies; therefore, determining the underlying genetic cause...
may help guide treatment decisions. Monogenic autoinflammatory conditions include the periodic fever syndromes (ie, familial Mediterranean fever, cryopyrinopathy-associated periodic syndrome, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, neonatal onset multisystem inflammatory disease or chronic infantile neurologic cutaneous and articular syndrome, tumor necrosis factor [TNF] receptor-associated periodic syndrome, hyper IgD syndrome/Mevalonate kinase deficiency), diseases with pyogenic lesions (ie, deficiency of IL-1 receptor antagonist [DIRA]; pyogenic arthritis, pyoderma gangrenosum and acne [PAPA]; Majeed syndrome), diseases with granulomatous lesions (ie, Blau syndrome), diseases with psoriasis (ie, deficiency of interleukin 36-receptor antagonist [DITRA]); diseases with panniculitis-induced lipodystrophy (JMP syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome [CANDLE], Nakajo-Nishimura syndrome [NNS], proteasome-associated autoinflammatory syndromes [PRAAS]). DITRA and CARD14-mediated psoriasis (CAMPS) both present with pustular skin lesions and early-onset inflammatory bowel disease (IBD). See Table 1 for a summary of genes included in this panel, associated diseases, and the mode of inheritance. NOD2-associated autoinflammatory disease (NAID), also known as Yao syndrome, is a newly-described clinical entity characterized by recurrent fever, dermatitis, and inflammatory arthritis along with GI symptoms in a majority of the patients. Variants in NOD2 have been associated with NAID; however, the variants that have been implicated to date are common variants that confer risk for development of the disorder and are not diagnostic. These common variants are not included in the report for this panel; however, a list of all common variants identified is available by request. While several of the autoinflammatory conditions, including those without a known genetic basis, are responsive to interleukin-1 (IL-1) blocking therapies, PRAAS, CANDLE, DITRA, and CAMPS are not responsive to IL-1 blockade. Anakinra, Rilonacept, and Canakinumab are several examples of medications that target IL-1. The NOD-like receptors (NLRs), which include 23 family members in humans, are an integral part of the innate immune system. NLRs are involved in the formation of the inflammasome, of which the NLRP3 (NALP3) inflammasome is most relevant to human disease and is responsible for activation of the proinflammatory cytokine IL-1 beta. Table 1. Genes included in the Autoinflammatory Gene Panel (listed in alphabetical order) GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER CARD14 Caspase recruitment domain-containing protein 14 isoform 1 607211 Rare AD Familial cold autoinflammatory syndrome 1 (FCAS1), Muckle-Wells syndrome; Neonatal onset multisystem inflammatory disease (NAID), also known as Yao syndrome, is a newly-described clinical entity characterized by recurrent fever, dermatitis, and inflammatory arthritis along with GI symptoms in a majority of the patients. Variants in NOD2 have been associated with NAID; however, the variants that have been implicated to date are common variants that confer risk for development of the disorder and are not diagnostic. These common variants are not included in the report for this panel; however, a list of all common variants identified is available by request. 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While several of the autoinflammatory conditions, including those without a known genetic basis, are responsive to interleukin-1 (IL-1) blocking therapies, PRAAS, CANDLE, DITRA, and CAMPS are not responsive to IL-1 blockade. Anakinra, Rilonacept, and Canakinumab are several examples of medications that target IL-1. The NOD-like receptors (NLRs), which include 23 family members in humans, are an integral part of the innate immune system. NLRs are involved in the formation of the inflammasome, of which the NLRP3 (NALP3) inflammasome is most relevant to human disease and is responsible for activation of the proinflammatory cytokine IL-1 beta. Table 1. 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finger-containing protein 1 isoform 2 610924 Rare AR Polyglucosan body myopathy 1 with or without immunodeficiency; chronic autoinflammation, invasive bacterial infections, muscle amylopectinosis SH3BP2 SH3 domain-binding protein 2 isoform 1a 602104 Rare AD Cherubism, autoinflammatory bone disease TNFRSF1A Tumor necrosis factor receptor superfamily member 1A precursor 191190 Primarily identified in Caucasians of western European ancestry AD Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) AD=autosomal dominant AR=autosomal recessive XL=X-linked

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of autoinflammatory syndromes and related disorders Establishing a diagnosis of autoinflammatory disease, and in some cases guiding management and allowing for surveillance of disease features Identification of pathogenic variants within genes known to be associated with autoinflammatory disorders allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


ARPKZ 35359 Autosomal Recessive Polycystic Kidney Disease (ARPKD), Full Gene Analysis, Varies

Clinical Information: Autosomal recessive polycystic kidney disease (ARPKD) is a disorder caused by mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene. The incidence of ARPKD is approximately 1:20,000 and the estimated carrier frequency in the general population is 1:70. ARPKD is characterized by enlarged echogenic kidneys, congenital hepatic fibrosis, and pulmonary hypoplasia (secondary to oligohydramnios [insufficient volume of amniotic fluid] in utero). Most individuals with ARPKD present during the neonatal period and, of those, nearly one-third die of respiratory insufficiency. Early diagnosis, in addition to initiation of renal replacement therapy (dialysis or transplantation) and respiratory support, increases the 10-year survival rate significantly. Presenting symptoms include bilateral palpable flank masses in infants and subsequent observation of typical findings on renal ultrasound, often within the clinical context of hypertension and prenatal oligohydramnios. In rarer cases, individuals may present during childhood or adulthood with hepatosplenomegaly. Of those who survive the neonatal period, one-third progress to end-stage renal disease and up to one-half develop chronic renal insufficiency. The PKHD1 gene maps to 6p12 and
includes 67 exons. The PKHD1 gene encodes a protein called fibrocystin, which is localized to the primary cilia and basal body of renal tubular and biliary epithelial cells. Because ARPKD is an autosomal recessive disease, affected individuals must carry 2 deleterious mutations within the PKHD1 gene. Although disease penetrance is 100%, intrafamilial variation in disease severity has been observed. Mutation detection is often difficult due to the large gene size and the prevalence of private mutations that span the entire length of the gene.

**Useful For:** Diagnosis of individuals suspected of having autosomal recessive polycystic kidney disease (ARPKD) Prenatal diagnosis if there is a high suspicion of ARPKD based on ultrasound findings Carrier testing of individuals with a family history of ARPKD but an affected individual is not available for testing or disease-causing mutations have not been identified

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FAVCG 57690**

**Avocado IgG**

**Interpretation:**

**Reference Values:**

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

**Clinical Information:**

Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to avocados Defining the allergen responsible for elicting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

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<th>Interpretation</th>
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<tbody>
<tr>
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<tr>
<td>1</td>
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<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 100 or</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
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</table>


FAZAT 91934
Azathioprine (Imuran) as 6-Mercaptopurine
Reference Values:

Units: ng/mL

Azathioprine is measured as the metabolite, 6-mercaptopurine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses produce 6-mercaptopurine serum concentrations of less than 1000 ng/ml.

CD40 89009
B-Cell CD40 Expression by Flow Cytometry, Blood

Clinical Information: The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer [NK] cells) and humoral (mediated by B cells) immunity. After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells. Decreased numbers or aberrant function of B cells result in humoral immune deficiency states with increased susceptibility to infections, and these may be either primary (genetic) or secondary immunodeficiencies. Secondary causes include medications, malignancies, infections, and autoimmune disorders (this does not cause immunodeficiency with increased infection). CD40 is a member of the tumor necrosis factor receptor superfamily, expressed on a wide range of cell types including B cells, macrophages, and dendritic cells.(1) CD40 is the receptor for CD40 ligand (CD40LG), a molecule predominantly expressed by activated CD4+ T cells.

CD40/CD40LG interaction is involved in the formation of memory B lymphocytes and promotes immunoglobulin (Ig) isotype switching.(1) CD40LG expression in T cells requires cellular activation, while CD40 is constitutively expressed on the surface of B cells and other antigen-presenting cells. Hyperimmunoglobulin M (hyper-IgM or HIGM) syndrome is a rare primary immunodeficiency
characterized by increased or normal levels of IgM with low IgG and/or IgA.(2) Patients with hyper-IgM syndromes may have genetic defects or mutations in 1 of several known genes. Some of these genes are CD40LG, CD40, AICDA (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and IKBKG (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma; also known as NEMO).(2) Not all cases of hyper-IgM syndrome fit into these known genetic defects. Mutations in CD40LG and IKBKG are inherited in an X-linked fashion, while mutations in the other 3 genes are autosomal recessive. Elevated IgM is only one of the features of NEMO deficiency and therefore, it is no longer classified exclusively with the hyper-IgM syndromes. Distinguishing between the different forms of hyper-IgM syndrome is very important because of differing prognoses. CD40 and CD40LG deficiency are among the more severe forms, which typically manifest in infancy or early childhood, and are characterized by an increased susceptibility to opportunistic pathogens (eg, Pneumocystis carinii, Cryptosporidium, and Toxoplasma gondii).(3) CD40 deficiency, also known as hyper-IgM type 3 (HIGM3), accounts for <1% of hyper-IgM syndromes. Flow cytometry analysis shows complete lack of CD40 expression on the B cells of these patients.(4) Intravenous injection with IgG is the treatment of choice along with immune reconstitution with hematopoietic cell transplantation. To date, all documented CD40-deficient patients have been diagnosed before age 1. Consequently, when used in the context of HIGM3, this test is only indicated in children (for diagnosis). In the case of CD40L deficiency, this test can be used for male patients or in females of child-bearing age (to identify carriers). A larger age spectrum has been reported with CD40L deficiency, ranging from infancy to early adulthood. CD40 expression on B cells is also an indicator of immune status (eg, after the use of biological immunomodulatory therapy for autoimmune disease, cancer and transplantation).

**Useful For:** Evaluating patients for hyper-IgM type 3 (HIGM3) syndrome due to defects in CD40, typically seen in patients <10 years of age Assessing B-cell immune competence in other clinical contexts, including autoimmunity, malignancy and transplantation

**Interpretation:** This assay is qualitative; CD40 expression is reported as present (normal) or absent (abnormal). Normal B cells express surface CD40 on the majority of cells. Hyper-IgM (HIGM3) syndrome patients typically do not express CD40 on the surface of B cells. Genotyping of CD40 is required for a definite diagnosis of HIGM3. Call 800-533-1710 for ordering assistance.

**Reference Values:**

Present (normal)


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**B-Cell Deficiency Primary Immunodeficiency Disorder Panel (34 genes), Next-Generation Sequencing, Varies**

**Clinical Information:** Primary B-cell disorders/humoral immunodeficiencies are characterized by an insufficient number of B-cells or impaired functioning/differentiation of B-cells. B-cell disorders account for approximately two-thirds of all genetic primary immunodeficiency disorders (PIDD) and may result in decrease or dysfunction of one or more isotypes of immunoglobulin, leading to increased susceptibility to infection, particularly bacterial infections such as sinopulmonary infections, gastrointestinal infections, otitis, skin infections, and conjunctivitis. In the absence of infection, patients may be asymptomatic and, thus, difficult to diagnose. In addition, primary B-cell disorders may result in lymphoproliferative disorders or be associated with autoimmune (AI) manifestations, including AI cytopenias, AI endocrine disorders, and AI enteropathy among others. There are several PIDD that also have an associated T-cell and/or other cellular immunodeficiency, in addition to the B-cell defects. In some disorders with agammaglobulinemia or hypogammaglobulinemia, patients may have reduced numbers of B-cells, resulting in a severe reduction in all antibody isotypes. Often, they present in the first few years of life.
with recurrent bacterial infections, a severe life-threatening bacterial infection (ie, meningitis, sepsis), and decreased lymphoid tissue (ie, small adenoids, tonsils, and lymph nodes in X-linked agammaglobulinemia, due to Bruton tyrosine kinase [BTK] gene mutations). Inheritance can be either X-linked (eg, due to variants in BTK), or autosomal recessive (eg, IGHM, CD79A, CD79B, IGLL1, BLNK, LRRC8A, and PIK3R1). B-cell lymphopenia with hypogammaglobulinemia can also be observed in WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis), which results from pathogenic gain-of-function variants in the CXCR4 gene. These patients also have severe peripheral neutropenia (ANC <500) with evidence of myelokathexis (neutrophil retention) in the bone marrow. In addition to recurrent infections (sinopulmonary, urinary tract, epidermis, deep soft tissue abscesses, skin), patients are also susceptible to warts and condyloma acuminata due to human papillomavirus (HPV) infection. Common variable immunodeficiency (CVID) is the most common adult humoral immunodeficiency disorder with an incidence of approximately 1:25,000 to 1:50,000. CVID may present with frequent and unusual infections during early childhood, adolescence, or adulthood. As per current diagnostic criteria, CVID is not considered in children younger than 4 years of age. In addition, a significant proportion of patients may have autoimmune or inflammatory manifestations, enlarged lymphoid tissues, granulomas, and an increased susceptibility to cancer. These patients typically have normal numbers of B-cells (<5% of CVID patients have less than 1% of B cells, which are considered to be due to early B cell defects), but have impaired terminal differentiation, resulting in decreased levels of IgG and IgA, with or without a decrease in IgM. Over two-thirds of patients have quantitative defects in switched memory B-cells. Some patients may also have quantitative and functional T-cell defects or NK cell deficiency. Patients with decreased naive T-cell numbers are considered to have late-onset combined immunodeficiency (LOCID). Genetic variants have been identified in several genes, including ICOS, TNFRSF13B (TACI), CD19, TNFRSF13C (BAFFR), MS4A1 (CD20), CR2 (CD21), CD81, LRBA, NFKB2, IKZF1 (IKAROS), among others, in a subset of CVID patients. However, the majority of these patients have unknown genetic defects and may have oligogenic or polygenic causes of disease.

Dysgammaglobulinemias including hyper-IgM syndrome and selective antibody deficiencies may also occur where a patient is either lacking a specific immunoglobulin isotype (eg, selective IgA deficiency) or a specific vaccine antibody response (impaired pneumococcal polysaccharide responsiveness) or may have an elevated/normal IgM level. Selective deficiencies (ie, IgA deficiency, IgG deficiency) may be due to variants in genes encoding immunoglobulin heavy or light chains. Selective IgA deficiency (sIgAD) is the most common PIDD with an incidence of 1:200 to 1:1000, depending on the cohort studied. Most patients with sIgAD are asymptomatic though some may have frequent infections. There is also a higher incidence of celiac disease in this group. Most patients with selective antibody deficiencies are treated if they have frequent infections in addition to impaired vaccine antibody responses. Some patients with sIgAD may have autoantibodies to IgA. Hyper IgM syndrome (mostly commonly due to variants in CD40LG but also due to other genes, eg, CD40, AICDA, PI3KCD, UNG) is characterized by an inability to switch from the production of IgM-type antibodies to IgG, IgA, or IgE isotypes. These individuals typically have a normal number of B-cells. Patients with CD40L and CD40 deficiency tend to present with severe opportunistic infections more reminiscent of a cellular immunodeficiency and, therefore, may also be considered as combined immunodeficiencies. Primary B-cell disorders may also result in lymphoproliferative diseases characterized by dysgammaglobulinemia/hypogammaglobulinemia, persistent or severe complications of Epstein-Barr virus (including hemophagocytic lymphohistiocytosis), and lymphoproliferative disorders (including malignant lymphomas). Lymphomas that are associated with these disorders are typically high-grade B-cell lymphomas, non-Hodgkin type, extranodal, and often involve the intestine. Inflammatory bowel disease has also been associated with some forms. Inheritance of these lymphoproliferative diseases can be X-linked or autosomal recessive. For example, X-linked lymphoproliferative disease (XLP) is due to pathogenic variants in SH2D1A (XLP-1), while autosomal recessive lymphoproliferative syndrome 2 is caused by pathogenic variants in TNFRSF7, which encodes CD27. Some of these lymphoproliferative disorders clinically manifest following infection, especially with Epstein-Barr virus (EBV). Post-meiotic segregation disorder, due to pathogenic variants in PMS2, leads to defective class switching from IgM and results in low serum IgG and IgA with elevated IgM. Patients also often demonstrate cafe-au-lait macules and are predisposed to several types of malignancy due to Lynch syndrome. PMS2 testing will be performed only for patients who demonstrate defective class switching. Table 1. Genes included in the B-cell Deficiency/Agammaglobulinemia/Lymphoproliferative Primary Immunodeficiency Gene Panel GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER AICDA Single-stranded DNA cytosine deaminase 605257 Unknown AR Immunodeficiency with hyper IgM, type 2 BLNK B-cell linker protein isoform 1 604515 Unknown AR Agammaglobulinemia BTK
Tyrosine-protein kinase BTK isoform 1 300300 1-9/million XL X-linked agammaglobulinemia CD79A B-cell antigen receptor complex-associated protein alpha chain isoform 1 precursor 112205 Unknown AR Agammaglobulinemia CD79B (B29) B-cell antigen receptor complex-associated protein beta chain isoform 1 precursor 147245 Unknown AR Agammaglobulinemia CARD11 Caspase recruitment domain-containing protein 11 607210 AR/AD Immunodeficiency 11 (AR), B-cell expansion with NFkB and T-cell anergy (AD) CD19 B-lymphocyte antigen CD19 isoform 2 precursor 107265 Unknown AR Common variable immunodeficiency (CVID) 3 CD27 (TNFRSF7) CD27 antigen precursor 186711 AR Lymphoproliferative syndrome 2 (CD27 deficiency) CD40 Tumor necrosis factor receptor superfamily member 5 isoform 1 precursor 109535 Unknown AR Immunodeficiency with hyper IgM CD40LG CD40 ligand 300386 2/million males XL Immunodeficiency with X-linked hyper IgM CD81 CD81 antigen isoform 1 186845 Unknown AR Common variable immunodeficiency (CVID) 6 CR2 (CD21) Complement receptor type 2 isoform 1 precursor 120650 Unknown AR Common variable immunodeficiency (CVID) 7 CXCRI C-X-C chemokine receptor type 4 isoform b 162643 AD Myelokathexis, isolated, WHIM syndrome (AD) GATA2 Endothelial transcription factor GATA-2 isoform 1 137295 AD Immunodeficiency 21, Emberger syndrome. A susceptibility to acute myeloid Leukemia and myelodysplastic syndrome ICOS Inducible T-cell costimulator precursor 604558 Unknown AR Common variable immunodeficiency (CVID) 1 IGHM IMMUNOGLOBULIN HEAVY CHAIN CONSTANT REGION MU 147020 Unknown AR Agammaglobulinemia IGLL1 (LAMBDA-5) Immunoglobulin lambda-like polypeptide 1 isoform a precursor 146770 Unknown AR Agammaglobulinemia IKZF1 (IKAROS) DNA-binding protein Ikaros isoform 2 603023 AD with incomplete penetrance Late-onset B-cell PIDÂ A LRBA Lipopolysaccharide-responsive and beige-like anchor protein isoform 2 606453 Unknown AR Common variable immunodeficiency (CVID) 8 with autoimmunity LRRRC8A Volume-regulated anion channel subunit LRRRC8A 608360 Unknown AD Agammaglobulinemia MALT1 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 isoform a 604860 AR Immunodeficiency 12 MS4A1 (CD20) B-lymphocyte antigen CD20 112210 AR Common variable immunodeficiency (CVID) 5 NFKB2 Nuclear factor NF-kappa-B p100 subunit isoform a 164012 Unknown AD Common variable immunodeficiency (CVID) 10 PIK3CD Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform 602839 Unknown AD Immunodeficiency 14, hyper IgM PIK3R1 Phosphatidylinositol 3-kinase regulatory subunit alpha isoform 1 171833 Unknown AR Agammaglobulinemia PLCG2 1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2 600220 Rare AD Autoinflammation, antibody deficiency, and immune dysregulation syndrome familial cold autoinflammatory syndrome PRKCD Protein kinase C delta type 3 176977 Unknown AR Autoimmune lymphoproliferative syndrome, type III RNF168 E3 ubiquitin-protein ligase RNF168 612688 AR RIDDLE syndrome SH2D1A SH2 domain-containing protein 1A isoform 1 300490 1/million males XL X-linked lymphoproliferative syndrome TCF3 (E47) Transcription factor E2-alpha isoform E12 147141 AD Agammaglobulinemia 8 TNFRSF13B (TACI) Tumor necrosis factor receptor superfamily member 13B 604907 Unknown AD or AR Common variable immunodeficiency (CVID) 2, immunoglobulin A deficiency TNFRSF13C Tumor necrosis factor receptor superfamily member 13C 606269 Unknown AD or AR Common variable immunodeficiency (CVID) 4 TNFSF12 (TWEAK) Tumor necrosis factor ligand superfamilies member 12 proprotein 602695 AD Low IgM and IgA UNG Uracil-DNA glycosylase isoform UNG2 191525 Unknown AR Immunodeficiency with hyper IgM syndrome, type 5 AD autosomal dominant AR autosomal recessive XL X-linked

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of primary B-cell deficiencies and related disorders. Patients with B cell immunodeficiency disorders who may have other clinical presentations, besides the humoral immune defect, such as inflammatory bowel disease, autoimmunity, or other as indicated above Establishing a diagnosis of a B-cell deficiency or related disorder, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for disease features allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools
may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**B-Cell Lymphoblastic Leukemia Monitoring, Minimal Residual Disease Detection, Flow Cytometry, Bone Marrow**

**Clinical Information:** B-cell lymphoblastic leukemia/lymphoma (B-ALL) is a neoplasm of precursor cells (lymphoblasts) committed to B-cell lineage. B-ALL is the most common acute leukemia in children and adolescents and also occurs in adults. Patients with B-ALL typically present with a high blast count in the peripheral blood and bone marrow replacement with the disease. The diagnosis of B-ALL is based on a combination of morphologic features showing primarily small blasts with open chromatin and high N:C ratio, and an immunophenotype showing immaturity (CD34 and/or TdT expression) associated with B-cell lineage markers (CD19, CD22, and CD79a). New therapeutic approaches in B-ALL have been increasingly successful. One of the most important predictors of the disease relapse is the ability to detect minimal residual disease (MRD) in the bone marrow specimens following induction phase of the therapy (day 28). Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD (at 0.002% sensitivity) is an important prognostic indicator in these patients. This test may also be used to establish an immunophenotypic fingerprint of tumor cells at diagnosis to monitor MRD in these patients after treatments or allogeneic stem cell transplant.

**Useful For:** Aids in monitoring a previously confirmed diagnosis of B-cell lymphoblastic leukemia

**Interpretation:** An interpretive report for the presence or absence of B-cell lymphoblastic leukemia (B-ALL) minimal residual disease (MRD) is provided. Patients who have detectable MRD by this assay are considered to have residual/recurrent B-ALL.

**Reference Values:**
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

**Clinical References:**
BLYM

**B-cell Lymphoma, FISH, Tissue**

**Clinical Information:** Mature B-cell lymphoma can be low grade, intermediate grade, or high grade, and the prognosis and clinical course are highly variable. Genetic abnormalities have emerged as one of the most important prognostic markers in B-cell lymphomas and can aid in diagnosis. Several chromosome abnormalities and variants of these abnormalities have been associated with various lymphoma subtypes (see table). Conventional chromosome studies cannot be employed on paraffin-embedded tissue, and molecular genetic analyses are often problematic in the study of lymphomas. FISH permits the detection of abnormal gene associated with various chromosome translocations and inversions in B-cell lymphoma (see table). Common Chromosome Abnormalities in B-cell Lymphomas Lymphoma Type Chromosome Abnormality FISH Probe Burkitt (pediatric, ≤18 years old) 8q24.1 rearrangement 5'/3' MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3'/5' BCL6 18q21 rearrangement 5'/3' BCL2 Diffuse large B-cell, Burkitt-like "double-hit" 8q24.1 rearrangement 5'/3' MYC t(8;14)(q24.1;q32) MYC/IGH ----Reflex: t(2;8)(p12;q24.1) IGK/MYC ----Reflex: t(8;22)(q24.1;q11.2) MYC/IGL ----Reflex: 3q27 rearrangement 3'/5' BCL6 ----Reflex: 18q21 rearrangement 3'/5' BCL2 Large BCL with IRF4 Rearranged 6p24.3 rearrangement 3'/5' IRF4 18q11 rearrangement 3'/5' BCL2 3q27 rearrangement 3'/5' BCL6 Follicular 18q21 rearrangement 3'/5' BCL2 3q27 rearrangement 3'/5' BCL6 Predominantly diffuse subtype only: deletion of 1p36 TNFRSF14/1q22 Mantle Cell t(11;14)(q13;q32) CCND1/IGH Blastoid subtype only: deletion of 17p TP53/D17Z1 Blastoid subtype only: 8q24.1 rearrangement 5'/3' MYC MAL1 18q21 rearrangement 5'/3' MAL1 Splenic Marginal Zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various B-cell lymphomas Tracking known chromosome abnormalities and response to therapy in patients with B-cell lymphomas

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone is supportive of a diagnosis of a B-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Edited by SH Swerdlow, E Campo, NL Harris. IARC, Lyon 2017

BLPF

**B-Cell Lymphoma, FISH, Varies**

**Clinical Information:** Lymphoid neoplasms are known to be complex and the prognosis and clinical course of patients with lymphoma is highly variable. Genetic abnormalities have emerged as one of the
most reliable criteria for categorizing lymphomas. Several chromosome abnormalities and variants of these abnormalities have been associated with various kinds of lymphoma (see Table). Common Chromosome Abnormalities in B-cell Lymphomas

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Chromosome Abnormality</th>
<th>FISH Probe</th>
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</thead>
</table>
| Burkitt (pediatric, ≤ 18 years old) | 8q24.1 rearrangement 5′/3′ MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3′/5′ BCL6 | t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3′/5′ BCL6 Diffuse large B-cell, "double-hit" or "triple hit" 8q24.1 rearrangement 3′/5′ MYC t(8;14)(q24.1;q32) MYC/IGH ----Reflex: t(2;8)(p12;q24.1) IGK/MYC ----Reflex: t(8;22)(q24.1;q11.2) MYC/IGL ----Reflex: 3q27 rearrangement 3′/5′ BCL6 Diffuse large B-cell, "double-hit" or "triple hit" 8q24.1 rearrangement 3′/5′ MYC t(8;14)(q24.1;q32) MYC/IGH ----Reflex: t(2;8)(p12;q24.1) IGK/MYC ----Reflex: t(8;22)(q24.1;q11.2) MYC/IGL ----Reflex: 3q27 rearrangement 3′/5′ BCL6Diffuse large B-cell, "double-hit" or "triple hit" 8q24.1 rearrangement 3′/5′ MYC t(8;14)(q24.1;q32) MYC/IGH ----Reflex: t(2;8)(p12;q24.1) IGK/MYC ----Reflex: t(8;22)(q24.1;q11.2) MYC/IGL ----Reflex: 3q27 rearrangement 3′/5′ BCL6Follicular 18q21 rearrangement 3′/5′ BCL2 3q27 rearrangement 3′/5′ BCL6Mantle Cell t(11;14)(q13;q32) CCND1/IGH ----Reflex: 11q13 rearrangement 5′/3′ CCND1 Blastoid subtype only: deletion of 17p TP53/D17Z1 Blastoid subtype only: 8q24.1 rearrangement 5′/3′ MYC Blastoid subtype only: t(8;14)(q24.1;q32) MYC/IGH Marginal Zone Lymphoma 18q21 rearrangement 5′/3′ MALT1 Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various B-cell lymphomas using blood or bone marrow specimens Tracking known chromosome abnormalities and response to therapy in patients with B-cell neoplasms

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone supports a diagnosis of a B-cell neoplasm; the specific abnormality detected may help subtype the neoplasm The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**IABCS 88800**

**B-Cell Phenotyping Profile for Immunodeficiency and Immune Competence Assessment, Blood**

**Clinical Information:** Quantitative Lymphocyte Subsets: T, B, and NK: Normal immunity requires a balance between the activities of various lymphocyte subpopulations with different effector and regulatory functions. Different immune cells can be characterized by unique surface membrane antigens described by a cluster of differentiation nomenclature (eg, CD3 is an antigen found on the surface of T lymphocytes). Abnormalities in the number and percent of T (CD3, CD4, CD8), B (CD19), and natural killer (CD16+CD56) lymphocytes have been described in a number of different diseases. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The US Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control...
distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. (2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening. (5) and during summer compared to winter. (6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Immune Assessment B Cell Subsets, Blood: The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer: NK cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are 3 subsets: marginal zone B cells (MZ or nonswitched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both, result in immune deficiency states and increased susceptibility to infections. These decreases may be either primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1 to 25,000 to 1 to 50,000. (1) CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years of age, or occasionally even later. Four different genetic defects have been associated with CVID including mutations in the ICOS, CD19, BAFF-R, and TACI genes. The first 3 genetic defects account for approximately 1% to 2%, and TACI mutations account for 8% to 15% of CVID cases. CVID is characterized by hypogammaglobulinemia usually involving most or all of the Ig classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections. (1,2) B-cell numbers may be normal or decreased. A minority of CVID patients (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency. (1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4 to CD8 ratio (<1). Studies have shown the clinical relevance of classifying CVID patients by assessing B-cell subsets, since changes in different B-cell subsets are associated with particular clinical phenotypes or presentations. (3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA. (5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects—mutations in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes. (5) Mutations in CD40L and NEMO are inherited in an X-linked fashion, while mutations in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increased in nonswitched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depicting therapies, such as Rituxan (Rituximab) and Zevalin (Ibritumomab tiuxetan). CVID Confirmation Flow Panel: The etiology of CVID is heterogeneous, but recently 4 genetic defects were described that are associated with the CVID phenotype. Specific mutations, all of which are expressed on B cells, have been implicated in the pathogenesis of CVID. These mutations encode for: (1) -ICOS-inducible costimulator expressed on activated T cells(1)
-TACI-transmembrane activator and CAML (calcium modulator and cyclophilin ligand) interactor(2)
-CD19(3) -BAFF-R-B cell activating factor belonging to the tumor necrosis factor (TNF) receptor family(4) Of these, the TACI mutations probably account for about 10% of all CVID cases. (2) Patients with mutations in the TACI gene are particularly prone to developing autoimmune disease, including cytopenias as well as lymphoproliferative disease. The other mutations each have been reported in only a handful of patients. The etiopathogenesis is still undefined in more than 50% of CVID patients. A BAFF-R defect should be suspected in patients with low to very low class switched and nonswitched memory B cells and very high numbers of transitional B cells (see IABC/87994 B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood). Class switching is the process that allows B cells, which possess IgD and IgM on their cell surface as a part of the antigen-binding complex, to produce IgA, IgE, or IgG antibodies. A TACI defect is suspected in patients with low IgM with normal to low switched B cells, with autoimmune and/or lymphoproliferative manifestations, and normal B cell responses to mitogens. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and
CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(5) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(6-8) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(6) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(9) and during summer compared to winter.(10) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Screening for common variable immunodeficiency (CVID) and hyper-IgM syndromes Assessing B-cell subset reconstitution after stem cell or bone marrow transplant Assessing response to B-cell-depleting immunotherapy Identifying defects in transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI) and B-cell-activating factor receptor (BAFF-R) in patients presenting with clinical symptoms and other laboratory features consistent with CVID

**Interpretation:** Quantitative Lymphocyte Subsets: T, B, and NK: When the CD4 count falls below 500 cells/mcL, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended. Immune Assessment B Cell Subsets, Blood: The assay provides quantitative information on the various B-cell subsets (percentage and absolute counts in cells/microliter). Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: -CD19+=B cells expressing CD19 as a percent of total lymphocytes -CD19+CD27+=total memory B cells -CD19+CD27+IgD+IgM+=marginal zone or nonswitched memory B cells -CD19+CD27+IgD-IgM+=IgM-only memory B cells -CD19+CD27+IgD-IgM+=class-switched memory B cells -CD19+IgM+=IgM B cells -CD19+CD38+IgM+=transitional B cells -CD19+CD38+IgM=plasmablasts -CD19+CD21+=mature B cells -CD19+CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes For isotype class-switching and memory B-cell analyses, the data will be reported as being consistent or not consistent with a defect in memory and/or class switching. If a defect is present in any of these B-cell subpopulations, further correlation with clinical presentation and additional functional, immunological, and genetic laboratory studies will be suggested. Since each of the 11 B-cell subsets listed above contributes to the diagnosis of common variable immunodeficiency (CVID) and hyper-IgM syndromes and provides further information on the likely specific genetic defect, all the B-cell subsets are carefully evaluated to determine if further testing is needed for confirmation, including functional assays and genotyping, which is then suggested as follow-up testing in the interpretive report as detailed below. If abnormalities are found in the B-cell phenotyping panel, the specimen will be reflexed to the CVID confirmation panel for assessment of defects in surface expression of B-cell-activating factor receptor (BAFF-R) and transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI) (2 genes/proteins associated with CVID). To conclusively determine if TACI mutations are present, the TACI mutation analysis test by gene sequencing can be ordered (TACIF / Transmembrane Activator and CAML Interactor [TACI] Gene, Full Gene Analysis). CVID Confirmation Flow Panel: BAFF-R is normally expressed on over 95% of B cells, while TACI is expressed on a smaller subset of B cells and a proportion of activated T cells. The lack of TACI or BAFF-R surface expression on the appropriate B-cell population is consistent with a CVID defect. Results will be interpreted in the context of the B-cell phenotyping results and correlation to clinical presentation will be recommended.

**Reference Values:** The appropriate age-related reference values will be provided on the report.


**COGBF**  
**B-Lymphoblastic Leukemia/Lymphoma, Children's Oncology Group Enrollment Testing, FISH, Varies**

**Clinical Information:** In the United States the incidence of acute lymphoblastic leukemia (ALL) is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0-19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). It has a peak incidence at 2 to 5 years of age. The incidence decreases with increasing age, before increasing again at around 50 years of age. ALL is slightly more common in males.
for enrollment in COG protocols for chromosome studies in pediatric patients with B-ALL and Ph-like ALL being considered as part of the Mayo Clinic Genomics Laboratory’s participation as a Children’s Oncology Group (COG) accredited laboratory for the performance of cytogenetic testing in pediatric patients being considered for enrollment in COG clinical trials and research. The laboratory is highly equipped to perform the time sensitive and critical cytogenetic testing necessary to assign risk stratification and facilitate enrollment in COG protocols. Each of the B-ALL genetic subgroups are important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), MLL (KMT2A) translocations, RUNX1 duplication/amplification or a hypodiploid clone is identified. In contrast, if ETV6/RUNX1 fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered. A newly recognized World Health Organization (WHO) entity BCR-ABL1-like ALL, also known as Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL), is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, and P2RY8. Patients that have failed on conventional therapies have demonstrated favorable responses to targeted therapies when rearrangements involving these specific gene regions have been identified. Evaluation of the MYC gene region is included in all diagnostic B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the BCL2 and BCL6 gene regions may be considered. Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome analysis (ie, t[12;21] associated with ETV6/RUNX1 fusion) is performed as required by COG and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intrachromosomal amplification of chromosome 21 (iAMP21). A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Common chromosome abnormalities in B-cell acute lymphoblastic leukemia Leukemia type Cytogenetic change Typical demographic Risk category B-cell acute lymphoblastic leukemia t(12;21)(p13;q22), ETV6(TEL)/RUNX1(AML1) Pediatric Favorable Hyperdiploidy Pediatric Favorable t(1:19)(q32:p13.3), PBX1/TCF3 Pediatric Intermediate t(9:22)(q34;q11.2), BCR/ABL1 Pediatric/adult Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A(p16) All ages Variable t(11q23;var), MLL All ages Unfavorable t(4:11)(q21;q23), AFF1(AF4)/MLL All ages Unfavorable t(9:11)(p22;q23), MLLT3(AF9)/MLL All ages Unfavorable t(11:19)(q23;p13.1), MLL/EML All ages Unfavorable t(9:11);(p12;q23), MLLT10/MLL All ages Unfavorable t(11;19)(q23;p13.3), MLL/MLLT1(ENL) All ages Unfavorable t(14q32;var), IGH All ages Variable t(X;14)(p22;q32)/t(Y;14)(p11;q32), CRLF2/IGH Adolescent/young adult Unfavorable t(Xp22.33;var) or t(Yp11.32;var), CRLF2 All ages Unfavorable t(Xp22.33;var) or t(Yp11.32;var), P2RY8 All ages Unfavorable t(Xp22.33;var) or t(Yp11.32;var), P2RY8 Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) t(1q25;var), ABL2 Pediatric/adolescent/young adult Low risk t(9q33;var), PDGFRB t(9p24.1;var), JAK2 t(9q34;var), ABL1 t(Xp22.33;var) or t(Yp11.32;var), CRLF2 t(Xp22.33;var) or t(Yp11.32;var), P2RY8 Useful For: Evaluation of pediatric bone marrow and peripheral blood specimens by fluorescence in situ hybridization probe analysis for classic rearrangements and chromosomal copy number changes associated with B lymphoblastic leukemia/lymphoma (B-ALL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) in patients being considered for enrollment in Children’s Oncology Group (COG) clinical trials and research protocols. As an adjunct to conventional chromosome studies in performed in pediatric patients with B-ALL and Ph-like ALL being considered for enrollment in COG protocols.
**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BALLF 35256**

**B-Lymphoblastic Leukemia/Lymphoma, FISH, Varies**

**Clinical Information:** In the United States the incidence of acute lymphoblastic leukemia (ALL) is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). It has a peak incidence at 2 to 5 years of age. The incidence decreases with increasing age, before increasing again at around 50 years of age. ALL is slightly more common in males than females. There is an increased incidence of ALL in individuals with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for ALL in children is about 90% and about 45% to 60% of adults have long-term disease-free survival. CRLF2/IGH rearrangements are more commonly observed in patients with Down syndrome or of Hispanic descent. Specific genetic abnormalities are identified in the majority of cases of B-ALL, either by conventional chromosome studies or fluorescence in situ hybridization (FISH) studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), MLL (KMT2A) translocations, RUNX1 duplication/amplification or a hypodiploid clone is identified. In contrast, if ETV6/RUNX1 fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered. A newly recognized World Health Organization (WHO) entity BCR-ABL1-like ALL or also known as Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, P2RY8, and deletions involving IKZF1. Patients who have failed conventional therapies have demonstrated favorable responses to targeted therapies when rearrangements involving these specific gene regions have been identified. Evaluation of the MYC gene region is included in all diagnostic B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the BCL2 and BCL6 gene regions may be considered. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the B-ALL clone for the important prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table.

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<thead>
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<th>Common Chromosome Abnormalities in B-Acute Lymphoblastic Leukemia Leukemia Type</th>
<th>Cytogenetic change</th>
<th>Typical demographic</th>
<th>Risk category</th>
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<tr>
<td>t(12;21)(p13;q22), ETV6(TEL)/RUNX1(AML1) Pediatric</td>
<td>Favorable</td>
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<td>Hyperdiploidy Pediatric Favorable</td>
<td>t(1;19)(q23;p13.3), PBX1/TCF3 All ages Intermediate</td>
<td>t(9;22)(q34;q11.2) BCR/ABL1 All ages Unfavorable iAMP21, RUNX1 Pediatric Unfavorable delet(9p), CDKN2A(p16) All ages Variable</td>
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<tr>
<td>AFF1(AF4)/MLL All ages Unfavorable</td>
<td>(q4;11)(q21;q23), MLLT4/MLL All ages Unfavorable t(6;11)(q27;q23), MLLT3(AF9)/MLL All ages Unfavorable</td>
<td>t(9;11)(p22;q23), MLLT10/MLL All ages Unfavorable</td>
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<td>t(9;11)(p22;q23)</td>
<td>t(10;11)(p12;q23), MLLT10/MLL All ages Unfavorable</td>
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</table>
Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with B-cell acute lymphoblastic leukemia (B-ALL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) Identifying and tracking known chromosome abnormalities in patients with B-ALL and Ph-like ALL and tracking response to therapy As an adjunct to conventional chromosome studies in patients with B-ALL and Ph-like ALL

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

Clinical References:

B-Type Natriuretic Peptide, Plasma

Clinical Information: B-type natriuretic peptide (BNP: formerly brain natriuretic peptide) is a 32-amino acid-ringed peptide secreted by the heart to regulate blood pressure and fluid balance.(1) BNP is stored in, and secreted predominantly from, membrane granules in the heart ventricles and is continuously released from the heart in response to both ventricle volume expansion and pressure overload.(2) The natriuretic peptide system and the renin-angiotensin system counteract each other in arterial pressure regulation. When arterial pressure decreases, the kidneys release renin, which activates angiotensinogen resulting in increased peripheral resistance of the arterioles, thus increasing arterial pressure. The natriuretic peptides counteract the effects of renin secretion, causing a reduction of blood pressure and extracellular fluid volume.(3) Both BNP and atrial natriuretic peptide (ANP) are activated by atrial and ventricular distension due to increased intracardiac pressure. These peptides have both natriuretic and diuretic properties: they raise sodium and water excretion by increasing the glomerular filtration rate and inhibiting sodium reabsorption by the kidney. The New York Heart Association (NYHA) developed a functional classification system for congestive heart failure (CHF) consisting of 4 stages based on the severity of the symptoms. Various studies have demonstrated that circulating BNP concentrations increase with the severity of CHF based on the NYHA classification.(4-6)

Useful For: Aiding in the diagnosis of congestive heart failure (CHF) The role of B-type natriuretic peptide in monitoring CHF therapy is under investigation

Interpretation: >Normal to <200 pg/mL: likely compensated congestive heart failure (CHF) > or =200 to < or =400 pg/mL: likely moderate CHF >400 pg/mL: likely moderate-to-severe CHF
natriuretic peptide (BNP) levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Interpretive Levels for CHF Functional Class 5th to 95th Percentile Median I 15 to 499 pg/mL II 10 to 1080 pg/mL II 222 pg/mL IV 147 to 1300 pg/mL All CHF 22 to >1300 pg/mL Elevation in BNP can occur due to right heart failure with cor pulmonale (200-500 pg/mL), pulmonary hypertension (300-500 pg/mL), and acute pulmonary embolism (150-500 pg/mL). Elevations also occur in patients with acute coronary syndromes.

### Reference Values:

**Males**

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<th>Reference Value</th>
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</tr>
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<tr>
<td>&gt; or =83 years</td>
<td>&lt; or =93 pg/mL</td>
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**Females**

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</tbody>
</table>

**Clinical References:**


**Babesia microti IgG Antibodies, Serum**

**Clinical Information:** Babesiosis is a zoonotic infection caused by the protozoan parasite Babesia microti. The infection is acquired by contact with Ixodes ticks carrying the parasite. The deer mouse is the animal reservoir and, overall, the epidemiology of this infection is much like that of Lyme disease. Babesiosis is most prevalent in the Northeast, upper Midwest, and Pacific Coast of the United States. Infectious forms (sporozoites) are injected during tick bites and the organism enters the vascular system where it infects red blood cells (RBC). In this intraerythrocytic stage, it becomes disseminated throughout the reticuloendothelial system. Asexual reproduction occurs in RBC, and daughter cells (merozoites) are formed that are liberated on rupture (hemolysis) of the RBC. Most cases of babesiosis are probably subclinical or mild, but the infection can be severe and life threatening, especially in older
or asplenic patients. Fever, fatigue, malaise, headache, and other flu-like symptoms occur most commonly. In the most severe cases, hemolysis, acute respiratory distress syndrome, and shock may develop. Patients may have hepatomegaly and splenomegaly. A serologic test can be used as an adjunct in the diagnosis and follow-up of babesiosis, when infection is chronic or persistent, or in seroepidemiologic surveys of the prevalence of the infection in certain populations. Babesiosis is usually diagnosed by observing the organisms in infected RBC on Giemsa-stained thin blood films of smeared peripheral blood. Serology may also be useful if the parasitemia is too low to detect or if the infection has cleared naturally or following treatment.

**Useful For:** An adjunct in the diagnosis of babesiosis Follow-up of documented babesiosis

**Interpretation:** A positive result of an indirect fluorescent antibody test (titer ≥ 1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2,560.

**Reference Values:**

<1:64

Reference values apply to all ages.

**Clinical References:**


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**Babesia species, Molecular Detection, PCR, Blood**

**Clinical Information:** Babesiosis is a tick-transmitted zoonosis caused by intraerythrocytic protozoa in the genus Babesia. Babesia microti is responsible for the vast majority of human cases in the United States, with most cases occurring along the Northeast Coast and the upper Midwestern states. A small number of cases of B duncani human infection have also been reported along Pacific Coast states from Washington to northern California, and B divergens/B divergens-like strains have been detected in humans in Missouri (MO-1 strain), Kentucky, and Washington. In Europe, B divergens and B venatorum are the primary causes of human babesiosis. Humans most commonly acquire infection through the bite of an infected tick. The most common tick vectors in the United States are Ixodes scapularis and Ixodes pacificus, while Ixodes ricinus and other ticks transmit the parasite in Europe and Asia. Less commonly, babesiosis may be acquired through blood transfusion and across the placenta from the mother to the fetus. Most patients with babesiosis are asymptomatic or have only a self-limited mild flu-like illness, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. Babesiosis is conventionally diagnosed through microscopic examination of Giemsa-stained thick and thin peripheral blood films looking for characteristic intraerythrocytic Babesia parasites. This method is relatively rapid, widely available, and capable of detecting (but not differentiating) human-infective Babesia species. It is also necessary for calculating the percentage of parasitemia which is used to predict prognosis, guide patient management, and monitor response to treatment. However, microscopic examination requires skilled microscopists and may be challenging in the setting of low parasitemia or prior drug therapy. Also, Babesia species may closely resemble those of Plasmodium falciparum. The Mayo Clinic real-time PCR assay provides a rapid and more sensitive alternative to blood film examination for detection and differentiation of B microti, B duncani, and B divergens/B divergens-like parasites. It does not cross-react with malaria parasites.

**Useful For:** An initial screening or confirmatory testing method for suspected babesiosis during the acute febrile stage of infection in patients from endemic areas, especially when Giemsa-stained peripheral blood smears do not reveal any organisms or the organism morphology is inconclusive.

**Interpretation:** A positive result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be
correlated with blood smear microscopy, serological results and clinical findings. A negative result indicates absence of detectable DNA from Babesia species in the specimen, but does not always rule out ongoing babesiosis in a seropositive person, since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in the evaluation of a patient presenting with an acute febrile illness following tick exposure include serologic tests for Lyme disease (Borrelia burgdorferi), and molecular detection (PCR) for ehrlichiosis/anaplasmosis. For patients who are past the acute stage of infection, serologic tests for these organisms should be ordered prior to PCR testing.

**Reference Values:**
Negative

**Clinical References:**

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**FBACS**

**Baclofen, Serum**

**Interpretation:** Serum concentrations required for therapeutic effects reportedly range from 0.08 - 0.40 mcg/mL.

**Reference Values:**
Reporting limit determined each analysis.

**Units:** mcg/mL

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**GENS**

**Bacterial Culture, Aerobic with Antimicrobial Susceptibilities, Varies**

**Clinical Information:** Sterile Body Fluids and Normally Sterile Tissues: In response to infection, fluid may accumulate in any body cavity. Wound, Abscess, Exudates: Skin and soft tissue infections can occur as a result of a break in the skin surface, or they can occur as complications of surgery, trauma, human, animal, or insect bites or diseases that interrupt a mucosal or skin surface. Specimen collection is of utmost importance for these specimen types. For most open lesions and abscesses, remove the superficial flora by decontaminating the skin before collecting a specimen from the advancing margin or base. A closed abscess is the specimen site of choice. Aspirate the abscess contents with a syringe. The specific anatomic site is required to establish possible contaminating flora in the area of specimen collection for appropriate reporting of culture results. For this reason, specimens should be labeled as to the specific anatomic source and to distinguish between â€œsurfaceâ€• and â€œdeep/surgicalâ€• specimens. Do not label only as â€œwound.â€• Antimicrobial susceptibility testing should be performed on pure culture isolates of pathogenic (or potentially pathogenic in special situations) bacteria grown from specimens that have been appropriately collected so as not to confuse clinically significant isolates with normal flora. Antimicrobial susceptibility testing determines the minimum inhibitory concentration (MIC) value of selected antimicrobial agents against isolated potentially pathogenic bacteria. The MIC is the lowest antimicrobial concentration (of a series of increasing concentrations) that inhibits growth of the bacterium. Agar dilution MIC testing is performed by testing for growth of bacteria on agar plates containing varying concentrations of antimicrobial agents. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute provides interpretive criteria for determining whether the MIC should be interpreted as...
susceptible, susceptible dose dependent, intermediate, non-susceptible, resistant, or epidemiological cutoff value (ECV).

**Useful For:** Detecting bacteria responsible for infections of sterile body fluids, tissues, or wounds. Determining the in vitro antimicrobial susceptibility of potentially pathogenic aerobic bacteria, if appropriate. This test is not intended for medicolegal use.

**Interpretation:** Any microorganism is considered significant and is reported when the anatomical source is considered sterile and no resident flora is expected. For specimens contaminated with the usual bacterial flora, bacteria that are potentially pathogenic are identified. A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. Refer to the Reference Values section for interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, non-susceptible, resistant, or epidemiological cutoff value: ECV).

**Reference Values:**
No growth or usual flora

Identification of probable pathogens

Results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, non-susceptible, or epidemiological cutoff value according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible (S):**
A category defined by a breakpoint that implies that isolates with an MIC at or below or a zone diameter at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of an antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Susceptible-Dose Dependent (SDD):**
A category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of a SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function.

**Intermediate (I):**
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and/or for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

**Resistant (R):**
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in...
treatment studies.

Nonsusceptible (NS):
A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MIC are above or the zone diameters are below the value indicated for the susceptible breakpoint should be reported as nonsusceptible.

Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MIC above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

Epidemiological Cutoff Value (ECV):
The minimal inhibitory concentration (MIC) that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency.

When an ECV is reported, the following comment will be included: "This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates [WITH / WITHOUT] acquired resistance; however, correlation with treatment outcome is unknown."


associated with lower respiratory tract infections are reported. For positive test results, pathogenic bacteria are identified. Cystic fibrosis (CF) patients may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results.

**Reference Values:**
- No growth or usual flora
- Identification of probable pathogens

**Clinical References:**

**SPUTS 60517**

**Bacterial Culture, Aerobic, Respiratory with Antimicrobial Susceptibilities, Varies**

**Clinical Information:** Common bacterial agents of acute pneumonia include Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, and members of the Enterobacteriaceae (eg, Escherichia coli, Klebsiella species, and Enterobacter species). Clinical history, physical examination, and chest X-ray are usually adequate for the diagnosis of pneumonia, and antimicrobial treatment is typically based on these findings. Culture of expectorated sputum is used by some for the evaluation of pneumonia, although controversy exists regarding this practice; both sensitivity and specificity of sputum cultures are generally regarded as poor (<50%). Specificity is improved by collecting expectorated purulent matter from the lower respiratory tract and avoiding mouth and oropharyngeal matter, thereby reducing contamination. Prior to culture, the specimen should be examined for the presence of white blood cells (evidence of purulent matter) and a paucity of squamous cells (evidence of minimal contamination by oral matter). Blood cultures should be performed to establish the definitive etiology of an associated pneumonia. However, only 20% to 30% of patients with bacterial pneumonia are bacteremic. Antimicrobial susceptibility testing should be performed on pure culture isolates of pathogenic (or potentially pathogenic in special situations) bacteria grown from specimens that have been appropriately collected so as not to confuse clinically significant isolates with normal flora. Antimicrobial susceptibility testing determines the minimum inhibitory concentration (MIC) value of selected antimicrobial agents against isolated potentially pathogenic bacteria. The MIC is the lowest antimicrobial concentration (of a series of increasing concentrations) that inhibits growth of the bacterium. Agar dilution MIC testing is performed by testing for growth of bacteria on agar plates containing varying concentrations of antimicrobial agents. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute provides interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value (ECV).

**Useful For:** Aiding the diagnosis of lower respiratory bacterial infections, including pneumonia

**Interpretation:** A negative test result is no growth of bacteria or growth of only usual flora. A negative result does not rule out all causes of infectious lung disease (see Cautions). Organisms associated with lower respiratory tract infections are reported. For positive test results, pathogenic bacteria are identified. Cystic fibrosis (CF) patients may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results. Refer to the Reference Values section for interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value: ECV).
**Reference Values:**

No growth or usual flora.

Identification of probable pathogens.

When antimicrobial susceptibilities are performed, results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, nonsusceptible, or epidemiological cutoff value according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible (S):**
A category defined by a breakpoint that implies that isolates with an MIC or a zone diameter at or below the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Susceptible-Dose Dependent (SDD):**
A category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of a SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function.

**Intermediate (I):**
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and/or tissue levels and for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

**Resistant (R):**
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

**Nonsusceptible (NS):**
A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above or the zone diameters are below the value indicated for the susceptible breakpoint should be reported as nonsusceptible.

Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

**Epidemiological Cutoff Value (ECV):**
The minimal inhibitory concentration (MIC) that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency.

When an ECV is reported, the following comment will be included: “This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates (WITH/WITHOUT) acquired resistance; however, correlation with treatment outcome is unknown.”


Bacterial Culture, Aerobic, Urine

Clinical Information: Urinary tract infection (UTI) encompasses a broad range of clinical entities that vary in their clinical presentation, degree of tissue invasion, epidemiologic setting, and antibiotic therapy requirements. There are 4 major types of UTIs: urethritis, cystitis, acute urethral syndrome, and pyelonephritis. UTIs may also be classified as uncomplicated or complicated. Escherichia coli is the leading cause of uncomplicated community-acquired UTI. Risk factors that predispose one to complicated UTIs include: underlying diseases that are associated with kidney infection (eg, diabetes), kidney stones, structural or functional urinary tract abnormalities, and indwelling urinary catheters. Another classification of UTIs is as upper UTI (related to the kidney, renal pelvis, or ureter) or lower UTI (urinary bladder and urethra). The classic symptoms of upper UTI are fever (often with chills) and flank pain; frequent painful urination, urgency, and dysuria are more often associated with lower UTI.

Useful For: Diagnosis of urinary tract infections Quantitative culture results may be helpful in discriminating contamination, colonization, and infection

Interpretation: In general, the isolation of more than 100,000 cfu/mL of a urinary pathogen is indicative of urinary tract infection (UTI). Isolation of 2 or more organisms above 10,000 cfu/mL may suggest specimen contamination. For specimens contaminated with the usual bacterial flora, bacteria that are potentially pathogenic are identified.

Reference Values:
No growth (Organism present <10,000 cfu/mL, or mixed flora.)
Identification of probable pathogens with colony count ranges

**Bacterial Culture, Aerobic, Varies**

**Clinical Information:** Sterile Body Fluids and Normally Sterile Tissues: In response to infection, fluid may accumulate in any body cavity. Wound, Abscess, Exudates: Skin and soft tissue infections can occur as a result of a break in the skin surface, as complications of surgery, from trauma; human, animal, or insect bites, or from diseases that interrupt a mucosal or skin surface. Specimen collection is of utmost importance for these specimen types. For most open lesions and abscesses, remove the superficial flora by decontaminating the skin before collecting a specimen from the advancing margin or base. A closed abscess is the specimen site of choice. Aspirate the abscess contents with a syringe. The specific anatomic site is required to establish possible contaminating flora in the area of specimen collection for appropriate reporting of culture results. For this reason, specimens should be labeled as to the specific anatomic source and to distinguish between表面/deep/surgical specimen specimens. Do not label only as wound.

**Useful For:** Detecting bacteria responsible for infections of sterile body fluids, tissues, or wounds

**Interpretation:** When no resident flora is present, any microorganism found is considered significant and is reported. For specimens contaminated with normal bacterial flora, bacteria that are potentially pathogenic are identified.

**Reference Values:**
No growth or usual flora
Identification of probable pathogens

**Clinical References:**

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**Bacterial Culture, Aerobic, with Antimicrobial Susceptibilities, Urine**

**Clinical Information:** Urinary tract infection (UTI) encompasses a broad range of clinical entities that vary in their clinical presentation, degree of tissue invasion, epidemiologic setting, and antibiotic therapy requirements. There are 4 major types of UTIs: urethritis, cystitis, acute urethral syndrome, and pyelonephritis. UTIs may also be classified as uncomplicated or complicated. Escherichia coli is the leading cause of uncomplicated community-acquired UTI. Risk factors that predispose one to complicated UTIs include: underlying diseases that are associated with kidney infection (eg, diabetes), kidney stones, structural or functional urinary tract abnormalities, and indwelling urinary catheters. Another classification of UTIs is as upper UTI (related to the kidney, renal pelvis, or ureter) or lower UTI (urinary bladder and urethra). The classic symptoms of upper UTI are fever (often with chills) and flank pain. Frequent painful urination, urgency, and dysuria are more often associated with lower UTI. Antimicrobial susceptibility testing determines the minimum inhibitory concentration (MIC) value of selected antimicrobial agents against isolated potentially pathogenic bacteria. The MIC is the lowest antimicrobial concentration (of a series of increasing concentrations) that inhibits growth of the bacterium. Agar dilution MIC testing is performed by testing for growth of bacteria on agar plates containing varying concentrations of antimicrobial agents. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute provides interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value (ECV).

**Useful For:** Diagnosis of urinary tract infections Quantitative culture results may be helpful in
Interpretation: In general, the isolation of more than 100,000 colony forming units (cfu)/mL of a urinary pathogen is indicative of urinary tract infection (UTI), however, pediatric patients (< or ≥2 years of age) may have symptomatic UTI at a lower threshold or more than 50,000 cfu/mL. Isolation of 2 or more organisms with more than 10,000 cfu/mL may suggest specimen contamination. For specimens contaminated with the usual bacterial flora, bacteria that are potentially pathogenic are identified. A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. Refer to the Reference Values section for interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value: ECV).

Reference Values:
No growth, Organism present <10,000 cfu/mL, or mixed flora.

Identification of probable pathogens with colony count ranges.

When antimicrobial susceptibilities are performed, results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, nonsusceptible, or epidemiological cutoff value according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

Susceptible (S):
A category defined by a breakpoint that implies that isolates with an MIC at or below or a zone diameter the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

Susceptible-Dose Dependent (SDD):
A category defined by a breakpoint that implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of a SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function.

Intermediate (I):
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and/or tissue levels and for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant (R):
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in
treatment studies.

Nonsusceptible (NS):
A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above or the zone diameters are below the value indicated for the susceptible breakpoint should be reported as nonsusceptible.

Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

Epidemiological Cutoff Value (ECV):
The minimal inhibitory concentration (MIC) that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency.

When an ECV is reported, the following comment will be included: "This MIC is consistent with the epidemiological cutoff value (ECV) observed in isolates (WITH/WITHOUT) acquired resistance; however, correlation with treatment outcome is unknown."


Clinical References:

Bacterial Culture, Anaerobic with Antimicrobial Susceptibilities, Varies

Clinical Information: Anaerobic bacteria are the greatest component of the human body's normal bacterial flora. Anaerobes colonize the skin, oral cavity, and genital urinary and lower gastrointestinal tracts, and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are compromised, in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes, and by alterations in membrane permeability and structure of penicillin-binding proteins. Susceptibility testing results are useful to clinicians because anaerobic bacteria are a significant cause of human infection, and they are often resistant to commonly used antimicrobials. Bacteroides and Parabacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are generally effective agents although resistance to clindamycin, and occasionally ertapenem, is increasing. The minimum inhibitory concentration (MIC) obtained during antimicrobial susceptibility testing is
helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. The MICs are accompanied by interpretive categories (ie, susceptible, intermediate, resistant, or epidemiological cutoff value (ECV) when applicable.

**Useful For:** Diagnosing anaerobic bacterial infections Directing antimicrobial therapy for anaerobic infections

**Interpretation:** Isolation of anaerobes in significant numbers from specimens collected under sterile conditions including blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with those organisms. A susceptible category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. For interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, intermediate, resistant, or epidemiological cutoff value [ECV]), see the Reference Values section.

**Reference Values:**
No growth

Identification of probable pathogens:
When antimicrobial susceptibilities are performed, results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, nonsusceptible, or epidemiological cutoff value according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible (S):**
A category defined by a breakpoint that implies that isolates with an MIC at or below or a zone diameter at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Intermediate (I):**
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

**Resistant (R):**
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

**Epidemiological Cutoff Value (ECV):**
The minimal inhibitory concentration (MIC) that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by Clinical and Laboratory Standards Institute (CLSI) or any regulatory agency.

When an ECV is reported, the following comment will be included: "This MIC is consistent with the
Epidemiological Cutoff Value (ECV) observed in isolates (WITH / WITHOUT) acquired resistance; however, correlation with treatment outcome is unknown.

(Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. 30th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2020)


Bacterial Culture, Anaerobic, Varies

Clinical Information: Anaerobic bacteria are the greatest component of the human body’s normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are penetrated as well as in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes as well as by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians. Bacteroides and Parabacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are generally effective agents although resistance to clindamycin, and occasionally ertapenem, is increasing.

Useful For: Diagnosing anaerobic bacterial infections

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

Reference Values:
No growth
Identification of probable pathogens


Bacterial Culture, Cystic Fibrosis with Antimicrobial Susceptibilities, Varies

Clinical Information: Life expectancy of patients with cystic fibrosis (CF) has increased steadily over the past 50 years, in large part due to improvements in the management of lung disease in this patient population. Still, chronic lung infection is responsible for 75% to 85% of deaths in patients with
CF. Appropriate treatment for the causative organism can reduce morbidity and mortality. The number of microbial species associated with CF lung disease is relatively limited. These include Pseudomonas aeruginosa (mucoid and nonmucoid), Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia, other non-fermenting Gram-negative rods, Haemophilus influenzae, and Streptococcus pneumoniae. Nontuberculous mycobacteria and Aspergillus species may also play a role in CF lung disease, in addition to common respiratory viruses. This culture is specifically designed and utilizes conventional and additional selective media (compared to non-CF respiratory cultures) to isolate bacteria commonly associated with pulmonary disease in patients with CF. In selected centers, lung transplantation is performed on patients with CF. This test is appropriate for lung transplant patients with underlying CF because they can continue to harbor the same types of organisms as they did prior to transplantation. Patients with CF may be colonized or chronically infected by these organisms over a long period of time. Antimicrobial susceptibility testing determines the minimal inhibitory concentration (MIC) value of selected antimicrobial agents against isolated potentially pathogenic bacteria. The MIC is the lowest antimicrobial concentration (of a series of increasing concentrations) that inhibits growth of the bacterium. Agar dilution MIC testing is performed by testing for growth of bacteria on agar plates containing varying concentrations of antimicrobial agents. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute provides interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value (ECV).

**Useful For:** Detection of aerobic bacterial pathogens in specimens from patients with cystic fibrosis

**Determining the in vitro antimicrobial susceptibility of potentially pathogenic aerobic bacteria, if appropriate**

**Interpretation:** A negative test result is no growth of bacteria or growth of only usual flora. A negative result does not rule out all causes of infectious lung disease (see Cautions). Organisms associated with lower respiratory tract infections are reported. For positive test results, pathogenic bacteria are identified. Patients with cystic fibrosis (CF) may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results. A susceptible category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. For interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or Epidemiological Cutoff Value: ECV), see Reference Values section.

**Reference Values:**

No growth or usual flora

Identification of probable pathogens:
Results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as "clinical breakpoints") are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, nonsusceptible, or epidemiological cutoff value according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible (S):**
A category defined by a breakpoint that implies that isolates with an MIC at or below or a zone diameter at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Susceptible-Dose Dependent (SDD):**
A category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD
category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved literature-supported dosage regimen, because higher exposure gives the highest probability of adequate coverage of a SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function.

Intermediate (I):
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant (R):
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Nonsusceptible (NS):
A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above or the zone diameters are below the value indicated for the susceptible breakpoint should be reported as nonsusceptible.

Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

Epidemiological Cutoff Value (ECV):
The minimal inhibitory concentration (MIC) that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency.

When an ECV is reported, the following comment will be included: "This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates (WITH / WITHOUT) acquired resistance; however, correlation with treatment outcome is unknown."

(Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. 30th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2020)

### CFRC 89653

**Bacterial Culture, Cystic Fibrosis, Respiratory**

**Clinical Information:** Life expectancy of patients with cystic fibrosis (CF) has increased steadily over the past 50 years, in large part due to improvements in the management of lung disease in this patient population. Still, chronic lung infection is responsible for 75% to 85% of deaths in patients with CF. Appropriate treatment for the causative organism can reduce morbidity and mortality. The number of microbial species associated with CF lung disease is relatively limited. These include Pseudomonas aeruginosa (mucoid and nonmucoid), Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia, other non-fermenting gram-negative rods, Haemophilus influenzae, and Streptococcus pneumoniae. Nontuberculous mycobacteria and Aspergillus species may also play a role in CF lung disease, in addition to common respiratory viruses. This culture is specifically designed and utilizes conventional and additional selective media (compared to non-CF respiratory cultures) to isolate bacteria commonly associated with pulmonary disease in patients with CF. In selected centers, lung transplantation is performed on patients with CF. This test is appropriate for lung transplant patients with underlying CF because they can continue to harbor the same types of organisms as they did pretransplantation. Patients with CF may be colonized or chronically infected by these organisms over a long period of time.

**Useful For:** Detection of aerobic bacterial pathogens in specimens from patients with cystic fibrosis

**Interpretation:** A negative test result is no growth of bacteria or growth of only usual flora. A negative result does not rule out all causes of infectious lung disease (see Cautions). Organisms associated with lower respiratory tract infections are reported. For positive test results, pathogenic bacteria are identified. Patients with cystic fibrosis may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results.

**Reference Values:**
- No growth or usual flora
- Identification of probable pathogens

**Clinical References:**

### BTWGS 65162

**Bacterial Typing, Whole Genome Sequencing, Varies**

**Clinical Information:** Bacterial strain typing may be useful for determining strain relatedness in the setting of possible nosocomial transmission or community outbreaks. Serial isolates obtained from the same patient may be typed to assess similarity. Typing may allow discrimination of 2 or more isolates of the same species, which can inform recognition of an outbreak, nosocomial transmission, or identify a potential source of infection in an individual patient. Pulse-field gel electrophoresis (PFGE) has traditionally been used for strain typing, but does not always discriminate between different bacterial strains (eg, 2 genetically dissimilar strains may have indistinguishable PFGE patterns). Whole genome sequencing offers a higher level of resolution of genetic relatedness of strains than PFGE does.

**Useful For:** Aiding in the investigation of a potential outbreak by a single bacterial species May assist in identification of recurrent infection in an individual patient

**Interpretation:** The genomic sequence of individual isolates will be determined and compared to the genomic sequences of the other cosubmitted isolates. The report will indicate the degree of relatedness between the isolates. A link to the interpretive report will be sent to the registered email address provided.

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 316
**Reference Values:**
Reported as isolates are "related", "possibly related", or "unrelated".

**Clinical References:**

**Bahia Grass, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Bahia grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's
Baker's Yeast, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to baker's yeast Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Bald Cypress, IgE, Serum

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

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

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

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<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Bamb 82879 Bamboo Shoot, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to bamboo shoots Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</tbody>
</table>

Reference values apply to all ages.


**FBANG**

**Banana IgG**

**Interpretation:**

**Reference Values:**

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

**BANA**

**Banana, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to bananas Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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Reference values apply to all ages.

Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,

BAP1 Immunostain, Technical Component Only

Clinical Information: BRCA1-associated protein 1 (BAP1) is a deubiquitinating enzyme that is a
member of the polycomb group proteins of transcriptional repressors and exhibits tumor suppressive
activity. BAP1 is located on chromosome 3p21 where loss of 1 copy of the gene and inactivating
mutations are associated with the increased risk and development of various tumors such as malignant
mesotheliomas, uveal melanomas, clear cell renal cell carcinoma, and esophageal squamous
carcinomas. In some of these cases, loss of nuclear staining for BAP1 has been reported.

Useful For: As part of a panel of immunostains where loss of staining can be used as a marker of
various neoplasms

Interpretation: This test includes only technical performance of the stain (no pathologist
interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the
context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology
Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with
the case is required. Additional specific stains may be requested as part of the pathology consultation,
and will be performed as necessary at the discretion of the Mayo pathologist. Â The positive and
negative controls are verified as showing appropriate immunoreactivity and documentation is retained at
Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant
quality control tissue is available upon request. Contact 855-516-8404. Â Interpretation of this test
should be performed in the context of the patient's clinical history and other diagnostic tests by a
qualified pathologist.

malignant mesothelioma, uveal and cutaneous melanoma, and MBAITS. J Transl Med 2012;10:179-185
Kapur P, Serie DJ, et al: Clear cell renal cell carcinoma subtypes identified by BAP1 and PBRM1
Galateau-Salle F: New markers for Separating Benign from Malignant Mesothelials: Are we there yet?
Barbiturates Confirmation, Chain of Custody, Random, Urine

Clinical Information: Barbiturates represent a class of drugs that were originally introduced as sleep inducers. Butalbital is also used to control severe headaches. Mephobarbital and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as "downers" to induce sleep after an amphetamine- or cocaine-induced "high." Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital. Chain-of-custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of a barbiturate in urine indicates use of one of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

Reference Values:
Negative

cutoff concentrations:

IMMUNOASSAY SCREEN
<200 ng/mL

BUTALBITAL BY GC-MS
<100 ng/mL

AMOBARBITAL BY GC-MS
<100 ng/mL

PENTOBARBITAL BY GC-MS
<100 ng/mL

SECOBARBITAL BY GC-MS
<100 ng/mL

PHENOBARBITAL BY GC-MS
<100 ng/mL

**Useful For:** Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital

**Interpretation:** The presence of a barbiturate in urine indicates use of one of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

**Reference Values:**
Negative

Cutoff concentrations:
- **BUTALBITAL BY GC-MS**
  - <100 ng/mL
- **AMOBARBITAL BY GC-MS**
  - <100 ng/mL
- **PENTOBARBITAL BY GC-MS**
  - <100 ng/mL
- **SECOBARBITAL BY GC-MS**
  - <100 ng/mL
- **PHENOBARBITAL BY GC-MS**
  - <100 ng/mL

**Clinical References:**

**FBARS**

**Barium, Serum**

**Reference Values:**
Units: ng/mL

Reference range has not been established.

**BGRS**

**Barley Grass, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Barley grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
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<td>0</td>
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<tr>
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<tr>
<td>2</td>
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<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
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<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FBARG 57578**

**Barley IgG**

**Interpretation:**

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

**BRLY 82687**

**Barley, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to barley Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
</tbody>
</table>
| 6             | > or =100            | Strongly positive Reference values apply to all ages.


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**FBART**

**Bartonella Antibody Panel, IFA CSF**

**Reference Values:**

**REFERENCE RANGE:** <1:1

**INTERPRETIVE CRITERIA:**

- <1:1 Antibody Not Detected
- > or = 1:1 Antibody Detected

Infection with Bartonella henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatis and febrile bacteremia syndrome. Infection with Bartonella quintana has been associated with trench fever and bacillary angiomatosis in both HIV positive and negative individuals.

IgG crossreactivity between B. henselae and B. Quintana may occur at any titer; however, the infecting species will typically have the higher IgG titer. Crossreactivity of IgM between the two species is limited and typically is not seen.

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecaly-produced specific antibody. However, interpreting results is complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps.

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**BART**

**Bartonella Antibody Panel, IgG and IgM, Serum**

**Clinical Information:** Bartonella henselae and Bartonella quintana are small, rod-shaped, pleomorphic, Gram-negative bacteria. The human body louse (Pediculus humanis) is the proposed vector for B quintana. No animal reservoir has been determined for B quintana. The domestic cat is believed to be both a reservoir and vector for B henselae. Cats may infect humans directly through scratches, bites, or licks; or indirectly through an arthropod vector. Humans remain the only host in which Bartonella infection leads to significant disease. The sight of entry for Bartonella is through...
openings in the skin. Microscopically, Bartonella lesions appear as rounded aggregates that proliferate rapidly. These aggregates are masses of Bartonella bacteria. Warthin-Starry staining has shown that Bartonella organisms can be present within the vacuoles of endothelial cells, in macrophages, and between cells in areas of necrosis. Occasionally organisms are seen in the lumens of vessels. While cutaneous lesions are common, disseminated tissue infection by Bartonella has been seen in the blood, lymph nodes, spleen, liver, bone marrow, and heart. B henselae has been associated with cat scratch disease (CSD), peliosis hepatitis (PH), bacillary angiomatosis (BA), and endocarditis. B quintana has been associated with trench fever, BA, and endocarditis. BA is a vascular proliferative disease usually involving the skin and regional lymph nodes. CSD begins as a cutaneous papule or pustule that usually develops within a week after an animal contact. Regional lymphadenopathy follows and is the predominant clinical feature of CSD. Trench fever, which was a significant problem during World War I and World War II, is characterized by a relapsing fever and severe pain in the shins. PH and febrile bacteremia syndrome are both syndromes that have afflicted patients with AIDS and patients who are immunocompromised. While trench fever and CSD are usually self-limiting illnesses, the other Bartonella-associated diseases can be life-threatening. Interest in B quintana and B henselae has recently increased since its increased prevalence in patients with AIDS, in transplant patients, and those with suppressed immunity.

**Useful For:** Diagnosis of Bartonella infection, especially in the context of a cat scratch

**Interpretation:** A positive immunofluorescence assay (IFA) IgM (titer >1:20) suggests a current infection with either Bartonella henselae or Bartonella quintana. A positive IgG (titer >1:128) suggests a current or previous infection. Increases in IgG titers in serial specimens suggest active infection. Normal serum specimens usually have an IgG titer of less than 1:128. However, 5% to 10% of healthy controls exhibit a B henselae and B quintana titer of 1:128. Sera from healthy volunteers rarely show titers of 1:256 or greater. IgM titers in normal serum are typically less than 1:20. IgM titers at 1:20 or greater have not been seen in the normal population. Molecular testing of tissue for Bartonella species nucleic acid is recommended in cases of suspected endocarditis.

**Reference Values:**

**Bartonella henselae**
- IgG: <1:128
- IgM: <1:20

**Bartonella quintana**
- IgG: <1:128
- IgM: <1:20

**Clinical References:**

**Bartonella, Molecular Detection, PCR, Blood**

**Clinical Information:** Bartonella henselae and B quintana are small, pleomorphic, gram-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. B henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. B quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue and serology. However, these methods may be nonspecific or falsely negative, especially in the early stages of disease. Evaluation of infected tissue or blood using PCR has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Clinic Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase (gltA) gene present in Bartonella species.

**Useful For:** Aiding in the diagnosis of Bartonella infection when Bartonella DNA would be expected to be present in blood, especially endocarditis
**Interpretation:** A positive result indicates the presence of Bartonella species DNA. A negative result indicates the absence of detectable Bartonella DNA, but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**BARRP 84440**

**Bartonella, Molecular Detection, PCR, Varies**

**Clinical Information:** Bartonella henselae and B quintana are small, pleomorphic Gram stain-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. B henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. B quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue or serology. However, these methods may be falsely negative or nonspecific, respectively. Culture is insensitive. Evaluation of infected tissue using PCR has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Clinic Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase gene present in Bartonella species.

**Useful For:** Aiding in the diagnosis of Bartonella infection

**Interpretation:** A positive result indicates the presence of Bartonella species DNA. A negative result indicates the absence of detectable Bartonella DNA, but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**BMAMA 113630**

**Basic Metabolic Panel, Serum**

**Clinical Information:** The basic metabolic panel measures 8 analytes and calculates an anion gap. It is used to assess kidney status, electrolyte, and acid/base balance, and blood glucose.

**Useful For:** Routine health monitoring or patient monitoring while hospitalized for information regarding metabolism, including the current kidney status, electrolyte, and acid/base balance, and blood glucose
**Interpretation:** Basic metabolic panel results are usually evaluated in conjunction with each other for patterns of results. A single abnormal test result could be indicative of something different than if more than 1 of the test results are abnormal. Many conditions will cause abnormal results including kidney failure, breathing problems, and diabetes-related complications.

**Reference Values:**

**SODIUM**
- <1 year: not established
- > or =1 year: 135-145 mmol/L

**POTASSIUM**
- <1 year: not established
- > or =1 year: 3.6-5.2 mmol/L

**CHLORIDE**
- <1 year: not established
- 1-17 years: 102-112 mmol/L
- > or =18 years: 98-107 mmol/L

**BICARBONATE**
- Males:
  - <1 year: not established
  - 1-2 years: 17-25 mmol/L
  - 3 years: 18-26 mmol/L
  - 4-5 years: 19-27 mmol/L
  - 6-7 years: 20-28 mmol/L
  - 8-17 years: 21-29 mmol/L
  - > or =18 years: 22-29 mmol/L
- Females:
  - <1 year: not established
  - 1-3 years: 18-25 mmol/L
  - 4-5 years: 19-26 mmol/L
  - 6-7 years: 20-27 mmol/L
  - 8-9 years: 21-28 mmol/L
  - > or =10 years: 22-29 mmol/L

**ANION GAP**
- <7 years: not established
- > or =7 years: 7-15

**BLOOD UREA NITROGEN**
- Males:
  - <12 months: not established
  - 1-17 years: 7-20 mg/dL
  - > or =18 years: 8-24 mg/dL
- Females:
  - <12 months: not established
  - 1-17 years: 7-20 mg/dL
  - > or =18 years: 6-21 mg/dL

**CREATININE**
- Males:
  - 0-11 months: 0.17-0.42 mg/dL
  - 1-5 years: 0.19-0.49 mg/dL
  - 6-10 years: 0.26-0.61 mg/dL
  - 11-17 years: 0.29-0.66 mg/dL
  - > or =18 years: 0.30-0.70 mg/dL
- Females:
  - 0-11 months: 0.14-0.36 mg/dL
  - 1-5 years: 0.17-0.40 mg/dL
  - 6-10 years: 0.20-0.51 mg/dL
  - 11-17 years: 0.22-0.53 mg/dL
  - > or =18 years: 0.23-0.60 mg/dL
11-14 years: 0.35-0.86 mg/dL  
> or =15 years: 0.74-1.35 mg/dL  

Females:  
0-11 months: 0.17-0.42 mg/dL  
1-5 years: 0.19-0.49 mg/dL  
6-10 years: 0.26-0.61 mg/dL  
11-15 years: 0.35-0.86 mg/dL  
> or =16 years: 0.59-1.04 mg/dL  

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)  
>60 mL/min/BSA  
Estimated GFR calculated using the 2009 CKD_EPI creatinine equation  

CALCIUM  
<1 year: 8.7-11.0 mg/dL  
1-17 years: 9.3-10.6 mg/dL  
18-59 years: 8.6-10.0 mg/dL  
60-90 years: 8.8-10.2 mg/dL  
>90 years: 8.2-9.6 mg/dL  

GLUCOSE  
0-11 months: not established  
> or =1 year: 70-140 mg/dL  


Basil IgG  
Interpretation:  

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

Basil, IgE, Serum  
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing the diagnosis of an allergy to basil Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

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

Reference Values:

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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
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<td>1</td>
<td>0.35-0.69</td>
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<td>6</td>
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</tr>
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FBBLE 57546

Bass Black (Sea Bass) (Centropristis striata) IgE

Interpretation: Class IgE(kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 Åèå,¬åøø 3.49 Moderate Positive 3 3.50 Åèå,¬åøø 17.49 Positive 4 17.50 Åèå,¬åøø 49.99 Strong Positive 5 50.00 Åèå,¬åøø 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:<0.35 kU/L

BAYL 82601

Bay Leaf, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing the diagnosis of an allergy to bay leaf. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode. - To confirm sensitization prior to beginning immunotherapy. - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

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

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<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


Bayberry/Wax Myrtle (Myrica spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 5 6 17.5 - 49.9 50.0 - 99.9 > or =100 Very High Positive Very High Positive Very High Positive

Reference Values:

<0.35 kU/L

BCL-2 Immunostain, Technical Component Only

Clinical Information: BCL-2 is in a family of regulators of apoptosis, which together control the balance between pro- and antiapoptotic signals. BCL-2 protein acts as an inhibitor of apoptosis. It is normally expressed in mantle zone B cells and T cells, with an intense perinuclear cytoplasmic pattern, but it is not expressed in reactive germinal center B cells. In the majority of cases of follicular lymphoma, the BCL-2 gene is involved in a translocation with IgH, t(14;18)(q32;q21), leading to overexpression of the BCL-2 protein. Thus, BCL-2 expression in germinal center B cells supports a diagnosis of follicular lymphoma.

Useful For: Classification of lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology.
Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**BCL-6 Immunostain, Technical Component Only**

**Clinical Information:** BCL-6 protein is a transcription factor expressed by follicle center B cells and other cells of the follicle center and is useful in the classification of lymphomas.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**BCOR Immunostain, Technical Component Only**

**Clinical Information:** Round cell sarcomas are a heterogeneous group of tumors which have diverse genetic abnormalities, clinical presentations and outcomes despite similar cytomorphology. The diagnosis of these emerging entities has relied on molecular tests until recent immunohistochemical screening markers. BCOR (BCL-6 interacting corepressor) is involved in suppressing gene expression by either interacting with BCL-6 or binding to PCGF1 (poly-comb-group RING finger homologue1) and inducing gene silencing by histone modification. BCOR immunohistochemistry is a highly sensitive marker in identifying round cell sarcomas with BCOR abnormalities.

**Useful For:** Helping in the distinction of a subset of primitive round cell sarcomas with BCOR rearrangements from other Ewing/Ewing-like sarcomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is
available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay, Varies

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myelogenous leukemia (CML) and “Philadelphia positive” acute lymphoblastic leukemia of B-cell lineage (Ph+ ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription polymerase chain reaction (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph+ ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR-ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph+ ALL can have alternative break-fusion events resulting in unusual BCR-ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR-ABL1 mRNA transcripts, this assay also can identify these rarer BCR-ABL1 transcript variants and is therefore a comprehensive screen for both usual and uncommon BCR-ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors however, this assay will not identify extremely rare and unexpected BCR-ABL1 events involving other exons (eg, case report level) and is therefore not absolutely specific, but is predicted to detect greater than 99.5% of BCR-ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR-ABL1 FISH or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR-ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which complementary methods cannot. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB / BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Varies; BA190 / BCR/ABL, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay, Varies). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality, or low cell number but it is not intended for quantitative or monitoring purposes.

Useful For: Diagnostic workup of patients with high probability of BCR-ABL1-positive hematopoietic neoplasms, predominantly chronic myeloid/myelogenous leukemia and acute lymphoblastic leukemia

Interpretation: An interpretive report will be provided. When positive, the test identifies which specific mRNA fusion variant is present to guide selection of an appropriate monitoring assay. If common p210 or p190 fusion variant detected, quantitative reflex will be performed. -Common fusion
variants detected: e13-a2 or e14-a2 (p210), e1-a2 (p190), and e6-a2 (p205*) - Rare fusion variants detected: e13-a3 (p210), e14-a3 (p210), e1-a3 (p190), e19-a2 (p230) - Potential rare fusions detected: e12-a3, e19-a3 *This is formerly observed as the e6-a2 (p185) fusion form

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**BA190**

**BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay, Varies**

**Clinical Information:**
mRNA transcribed from BCR/ABL1 (fusion of the breakpoint cluster region gene [BCR] at chromosome 22q11 to the Abelson gene [ABL1] at chromosome 9q34) is detected in all patients with chronic myeloid leukemia (CML) and a subset of patients with both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Although breakpoints in the BCR and ABL1 genes may occur in a variety of locations, splicing of the primary RNA transcripts result in only 8 fusion site variants (e1/a2, e6/a2, e13/a2, e14/a2, e19/a2, and e1/a3, e13/a3, e14/a3), which incorporate the entire sequence of the exons on both sides of the fusion site. The e1/a2 and e1/a3 fusion forms produce a 190-kDa protein designated p190. This BCR/ABL1 protein form is found in approximately 75% of patients with childhood ALL and approximately 50% of patients with adult ALL, with the majority arising from e1/a2 mRNA. The p190 is also the predominant fusion form in a small subset of patients with CML, although the vast majority of CML cases contain the p210 protein, typically from e13/a2 or e14/a2 mRNA fusions. Other fusion forms are very rare. Quantitative reverse-transcription PCR (qRT-PCR) is the most sensitive method for monitoring BCR/ABL1 levels during treatment. This test detects mRNA coding for the most common p190 fusion form (e1/a2).

**Useful For:** Monitoring response to therapy in patients with known e1/a2 BCR/ABL1 (p190) fusion forms

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
The presence or absence of the BCR/ABL1 mRNA fusion form producing the p190 fusion protein is reported. If positive, the level is reported as the ratio of BCR/ABL1 (p190) transcript to ABL1 transcript in the form of a percentage.

**Clinical References:**

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**B190R**

**BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Reflex, Varies**

**Clinical Information:** The t(9;22)/BCR-ABL1 abnormality is associated with chronic myeloid
leukemia (CML) and "Philadelphia positive" acute lymphoblastic leukemia of B-cell lineage (Ph+ ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription PCR (RT-PCR) technique. In CML, breakpoints in BCR nearly always result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph+ ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein, although some ALL patients may alternatively present with the e13/e14-a2 (p210) type fusion. This assay provides information at the time of diagnosis regarding the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. If positive, the reflex test will follow to provide an initial quantitative level of the specific BCR-ABL1 transcript. For example, when positive for the e1-a2 (p190) type mRNA, the reflex test provides a corresponding p190 quantitative value. Results from this test are also useful to determine the correct quantitative assay for subsequent monitoring of transcript levels (ie, p190 or p210) during tyrosine kinase inhibitor therapy.

**Useful For:** Diagnostic workup of patients with a high probability of BCR-ABL1-positive hematopoietic neoplasms, particularly acute lymphoblastic leukemia (B-lymphoblastic leukemia), to provide a pretreatment quantitative level of BCR-ABL1 mRNA transcript if the initial diagnostic RT-PCR screen is positive. When positive, the reflex test provides a quantitative value for the corresponding e1-a2 (p190) BCR-ABL1 mRNA fusion variant.

**Interpretation:** An interpretive report will be provided under the BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay, Varies.

**Reference Values:**
Only orderable as a reflex. For more information see BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay, Varies.

**BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Varies**

**Clinical Information:** Chronic myeloid leukemia (CML) is a hematopoietic stem cell neoplasm included in the broader diagnostic category of myeloproliferative neoplasms. CML is consistently associated with fusion of the breakpoint cluster region gene (BCR) at chromosome 22q11 to the Abelson gene (ABL1) at chromosome 9q23. This fusion is designated BCR/ABL1 and may be seen on routine karyotype as the Philadelphia chromosome. Although various breakpoints within the BCR and ABL1 genes have been described, more than 95% of CMLs contain a consistent mRNA transcript in which either the BCR exon 13 (e13) or BCR exon 14 (e14) is fused to the ABL1 exon 2 (a2), yielding fusion forms e13/a2 and e14/a2, respectively. The e13/a2 and e14/a2 fusion forms produce a 210-kDa protein (p210). The p210 fusion protein is an abnormal tyrosine kinase known to be critical for the clinical and pathologic features of CML, and agents that block the tyrosine kinase activity (ie, tyrosine kinase inhibitors or TKI, such as imatinib mesylate) have been used successfully for treatment. Monitoring the level of BCR/ABL1 mRNA in CML patients during treatment is helpful for both prognosis and management of therapy. (1-3) Rising BCR/ABL1 mRNA levels following attainment of critical therapeutic milestones (see Clinical References) can be indicative of acquired resistance mutations involving the ABL1 portion of the BCR/ABL1 fusion gene. Quantitative reverse-transcription PCR (qRT-PCR) is the most sensitive method for monitoring BCR-ABL1 levels during treatment. This test detects the BCR/ABL1 mRNA fusion forms found in CML (e13/a2 and e14/a2).

**Useful For:** Monitoring response to therapy in patients with chronic myeloid leukemia who are known to have the e13/a2 or e14/a2 BCR/ABL1 fusion transcript forms.
Interpretation: An interpretive report will be provided. When BCR/ABL1 mRNA is present, quantitative results are reported on the international scale (IS), established from data originally reported in the IRIS (International Randomized Study of Interferon versus STI571) trial involving newly diagnosed chronic myeloid leukemia patients. Using the IS, a result of less than 0.1% BCR/ABL1 (p210):ABL1 is equivalent to a major molecular remission. This value is also designated on a log scale (Molecular Response, MR) as MR3. For further discussion of the international scale, see Clinical References.

Reference Values:
The presence or absence of BCR/ABL1 mRNA fusion form e13/e14-a2 producing the p210 fusion protein is identified. If positive, the quantitative level is reported as the normalized ratio of BCR/ABL1 (p210) to endogenous ABL1 mRNA with conversion to a percentage referenced to the international scale (IS), on which 0.1% BCR/ABL1:ABL1 (also represented on a log scale as Molecular Response 3, or MR3) is designated as a major molecular response (MMR) threshold.

BCR/ABL1, Qualitative, Diagnostic Assay, Varies

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myelogenous leukemia (CML) and "Philadelphia-positive" acute lymphoblastic leukemia of B-cell lineage (Ph+ ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription-PCR (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210-kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph+ ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR-ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph+ ALL can have alternative break-fusion events resulting in unusual BCR-ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR-ABL1 mRNA transcripts, this assay also can identify these rarer BCR-ABL1 transcript variants and is, therefore, a comprehensive screen for both usual and uncommon BCR-ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors, however, this assay will not identify extremely rare and unexpected BCR-ABL1 events involving other exons (eg, case report level) and is, therefore, not absolutely specific, but is predicted to detect more than 99.5% of BCR-ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR-ABL1 FISH or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR-ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which cannot be done by complementary methods. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB / BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Varies; BA190 / BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay, Varies). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality, or low cell number, but it is not intended for quantitative or monitoring purposes.

Useful For: Diagnostic workup of patients with a high probability of BCR-ABL1-positive hematopoietic neoplasms, predominantly chronic myelogenous leukemia and acute lymphoblastic leukemia

Interpretation: An interpretive report will be provided. When positive, the test identifies the specific mRNA fusion variant present to guide selection of an appropriate monitoring assay. Monitoring is available for common p210 or p190 fusion variant detected. -Common fusion variants detected: e13-a2 or e14-a2 (p210), e1-a2 (p190), and e6-a2 (p205*) -Rare fusion variants detected: e13-a3 (p210), e14-a3 (p210), e1-a3 (p190), e19-a2 (p230) -Potential rare fusions detected: e12-a3, e19-a3 *This is formerly observed as the e6-a2 (p185) fusion form.

Reference Values: A qualitative result is provided that indicates the presence or absence of BCR/ABL1 mRNA. When positive, the fusion variant is also reported.

**Clinical Information:** Chronic myelogenous leukemia (CML) is characterized by the presence of the t(9:22) BCR/ABL1 abnormality, resulting in formation of a fusion BCR/ABL1 mRNA and protein. The ABL1 component of this oncoprotein contains tyrosine kinase activity and is thought to play a central role in the proliferative phenotype of this leukemia. Recent advances have resulted in a number of therapeutic drugs that inhibit the ABL1 tyrosine kinase, as well as other protein tyrosine kinases. Imatinib mesylate (Gleevec, Novartis) is the prototype of these tyrosine kinase inhibitors (TKIs), which are capable of inducing durable hematologic and (in most patients) cytogenetic remissions. Unfortunately, a significant subset of patients can develop functional resistance to TKIs, due in a large number of cases (approximately 50%) to the acquisition of point mutations in the kinase domain (KD) of the chimeric ABL1 gene. To date, over 50 distinct mutations have been described, although a smaller subset of these (<20) account for the majority of patients with clinical resistance to TKIs, or have well documented in vitro data in the published literature. Recognition of TKI resistance is important in CML, as the effect of some mutations can be overcome by increasing imatinib dosage, whereas others require switching to either a different (second-generation) TKI, or alternative therapy. The common T315I KD mutation is particularly important, given that this alteration confers pan-resistance to all currently employed TKIs except ponatinib. Typically, TKI resistance is suspected in a CML patient who shows loss of initial therapeutic response (eg, cytogenetic relapse), or a significant and sustained increase in molecular BCR/ABL1 quantitative levels. Similar considerations are also present in patients with Philadelphia chromosome positive B-cell acute lymphoblastic leukemia, who can also be treated using TKI therapy. Point mutations in the oncogenic BCR/ABL1 are typically detected by direct sequencing of PCR products, following RT-PCR amplification of the BCR/ABL mRNA transcript from a peripheral blood specimen. This approach ensures comprehensive screening of the clinically relevant KD region. Because this technique requires inclusion of a longer region of ABL1 in the BCR/ABL1 RT-PCR product, low levels of the BCR/ABL1 mRNA transcript (below 0.01% normalized BCR/ABL1 on the International Scale; IS) may not be efficiently amplified (in contrast to similar amplicons generated by quantitative RT-PCR for diagnosis or monitoring).

**Useful For:** Evaluating patients with chronic myelogenous leukemia and Philadelphia chromosome positive B-cell acute lymphoblastic leukemia receiving tyrosine kinase inhibitor (TKI) therapy, who are apparently failing treatment. Preferred initial test to identify the presence of acquired BCR-ABL1 mutations associated with TKI-resistance

**Interpretation:** The presence of one or more point mutations in the translocated portion of the ABL1 region of the BCR/ABL1 fusion mRNA is considered a positive result, indicating tyrosine kinase inhibitor (TKI) resistance. The specific type of mutation may influence the sensitivity to a specific TKI, and could be useful in guiding therapeutic options for an individual patient.

**Reference Values:**
An interpretive report will be provided.

Bean Black (Phaseolus spp) IgE

**Interpretation:**
- **Class IgE (kU/L) Comment**
  0  <0.35 Below Detection
  1  0.35  Low Positive
  2  0.70  Moderate Positive
  3  3.50  High Positive
  4  17.50  Very High Positive
  5  50.00  Strong Positive
  6  >99.99  Very Strong Positive

**Reference Values:**
- <0.35 kU/L

Bean Coffee Green IgG

**Interpretation:**

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

Bean Green/String IgG

**Interpretation:**

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

Bean Kidney IgG

**Interpretation:**

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

Bean Lima (Phaseolus limensis) IgE

**Interpretation:**
- **Class IgE (kU/L) Comment**
  0  <0.10 Negative
  1  0.10 - 0.34 Equivocal/Borderline
  2  0.35 - 0.69 Low Positive
  3  3.50 - 17.49 Moderate Positive
  4  17.50 - 49.99 High Positive
  5  50.00 - 99.99 Very High Positive

**Reference Values:**
- <0.35 kU/L
**Bean Navy/White (Phaseolus vulgaris) IgE**

**Interpretation:**

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<td>0.70</td>
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<tr>
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<td>Low Positive</td>
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<td>0.70-3.49</td>
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</table>

**Reference Values:**

<0.35 kU/L

**Bean Navy/White IgG**

**Interpretation:**

**Reference Values:**

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

**Beckwith-Wiedemann Syndrome/Russell-Silver Syndrome, Molecular Analysis, Varies**

**Clinical Information:**

Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Current data suggest that the etiology of BWS is due to dysregulation of imprinted genes in the 11p15 region of chromosome 11, including H19 (maternally expressed), LIT1 (official symbol KCNQ1OT1; paternally expressed), IGF2 (paternally expressed), and CDKN1C (aliases p57 and KIP2; maternally expressed). Expression of these genes is controlled by 2 imprinting centers (IC). Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is often due to inherited point alterations in CDKN1C or an unknown cause. The etiology of sporadic cases includes: -Hypomethylation of imprinting center 2 (IC2) (LIT1): approximately 50% to 60% -Paternal uniparental disomy of chromosome 11: approximately 10% to 20% -Hypermethylation of imprinting center 1 (IC1) (H19): approximately 2% to 7% -Unknown: approximately 10% to 20% -Point alteration in CDKN1C: approximately 5% to 10% -Cytogenetic abnormality: approximately 1% to 2% -Differentially methylated region 1 (DMR1) or DMR2 microdeletion: rare The clinical presentation of BWS is dependent on which gene in the 11p15 region is involved. The risk for cancer has been shown to be significantly higher in patients with abnormal methylation of IC1 (H19) versus IC2 (LIT1). In patients with abnormal methylation of IC2 (LIT1), abdominal wall defects and overgrowth are seen at a higher frequency. Russell-Silver syndrome (RSS) is a rare genetic condition with an incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth retardation with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include cafe au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia. Although clinical diagnostic criteria have been developed, it has been demonstrated that many patients with molecularly confirmed RSS do not meet strict clinical diagnostic criteria for RSS. Therefore, most groups recommend a relatively low threshold for considering molecular testing in suspected cases of RSS. RSS is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes: -Hypomethylation of
IC1 (H19): approximately 30% to 50% - Maternal uniparental disomy (UPD) of chromosome 7: approximately 5% to 10%* - 11p15.5 duplications: rare - Chromosome 7 duplications: rare* *Note that this test does not detect chromosome 7 UPD. However, testing is available; order UNIPD / Uniparental Disomy, Varies. The clinical phenotype of RSS has been associated with the specific underlying molecular etiology. Patients with hypomethylation of IC1 (H19) are more likely to exhibit "classic" RSS phenotype (ie, severe intrauterine growth retardation, postnatal growth retardation, and asymmetry), while patients with maternal UPD7 often show a milder clinical phenotype. Despite these general genotype-phenotype correlations, many exceptions have been reported. Methylation abnormalities of IC1 (H19) and IC2 (LIT1) can be detected by methylation-sensitive multiple ligation-dependent probe amplification. While testing can determine methylation status, it does not identify the mechanism responsible for the methylation defect (such as paternal uniparental disomy or cytogenetic abnormalities). Hypomethylation of IC2 (LIT1) is hypothesized to silence the expression of a number of maternally expressed genes, including CDKN1C. Hypermethylation of IC1 is hypothesized to silence the expression of H19, while also resulting in overexpression of IGF2. Absence of CDKN1C and H19 expression, in addition to overexpression of IGF2, is postulated to contribute to the clinical phenotype of BWS. Hypomethylation of IC1 is hypothesized to result in overexpression of H19 and underexpression of the IGF2, which is thought to contribute to the clinical phenotype of RSS.

**Useful For:** Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome (BWS) or Russell-Silver syndrome (RSS) Prenatal diagnosis if there is a high suspicion of BWS/RSS based on ultrasound findings or in families at risk for BWS/RSS

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BEECH 82669**

**Beech, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to beech Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
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<td>2</td>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Beef IgG**

**Interpretation:**

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

**Beef, IgE, Serum**

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

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
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<th>IgE kU/L</th>
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<tbody>
<tr>
<td>0</td>
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Reference values apply to all ages.


**Beet Root IgG**

**Interpretation:**

**Reference Values:**

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

**Beets (Beetroot), IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to beets Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**FPHEN 91136**

**Benzene as Phenol, Occupational Exposure, Urine**

**Reference Values:**

Creatinine: >50 mg/dL

Phenol: mg/L
Phenol: mg/G creat

Normal (unexposed population):
less than 10 mg/L

Exposed:
Biological Exposure Index (BEI): 50 mg/g creatinine (End of Shift)

Toxic:
Not Established

**FBEN 90294**

**Benzene, Occupational Exposure, Blood**

**Reference Values:**

Units: mg/L

Normal (unexposed population):
None detected
Exposed (end-of-shift):
Blood benzene concentrations of greater than 0.1 mg/L correlate with exposure to greater than 10 ppm benzene in air.
Toxic:
Blood benzene concentrations greater than 0.90 mg/L have been observed in fatal cases of benzene exposure.
Benzodiazepines Confirmation, Chain of Custody, Random, Urine

Clinical Information: Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most commonly prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. This includes a record of the disposition of a specimen to document the personnel who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug use involving benzodiazepines such as alprazolam, chlordiazepoxide, clonazepam, diazepam, midazolam, oxazepam, temazepam, clobazam, flunitrazepam, flurazepam, lorazepam, prazepam, triazolam, and zolpidem, in urine specimens handled through the chain-of-custody process

Interpretation: Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: Alprazolam, Alpha-hydroxyalprazolam (metabolite of alprazolam), Chlordiazepoxide, Clonazepam, 7-Aminoclonazepam (metabolite of clonazepam), Diazepam (separate prescribable drug and metabolite of medazepam), Nordiazepam (metabolite of clorazepate, halazepam, prazepam, diazepam and medazepam), Midazolam, Alpha-hydroxy midazolam (metabolite of midazolam), Oxazepam (separate prescribable drug and metabolite of clorazepate, halazepam, prazepam, medazepam, temazepam, and diazepam), Temazepam (separate prescribable drug and metabolite of medazepam and diazepam), Clobazam, N-Desmethylclobazam (metabolite of clobazam), Flunitrazepam, 7-Minoflunitrazepam (metabolite of flunitrazepam), Flurazepam, 2-Hydroxy ethyl flurazepam (metabolite of flurazepam), Lorazepam, Prazepam, Triazolam, Alpha-hydroxy triazolam (metabolite of triazolam), Zolpidem, Zolpidem phenyl-4-carboxylic acid (metabolite of zolpidem). The clearance half-life of long-acting benzodiazepines is more than 24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5 to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Clinic Laboratories Drugs of Abuse Testing Guide at https://www.mayocliniclabs.com/test-info/drug-book/index.html for additional information including metabolism, clearance (half-life), and approximate detection times.

Reference Values:
Negative

Cutoff concentrations:
- Alprazolam by LC-MS/MS: 10 ng/mL
- Alpha-Hydroxyalprazolam by LC-MS/MS: 10 ng/mL
- Chlordiazepoxide by LC-MS/MS: 10 ng/mL
- Clonazepam by LC-MS/MS: 10 ng/mL
- 7-Aminoclonazepam by LC-MS/MS: 10 ng/mL
- Diazepam by LC-MS/MS: 10 ng/mL
- Nordiazepam by LC-MS/MS: 10 ng/mL
- Midazolam by LC-MS/MS: 10 ng/mL
- Alpha-Hydroxy Midazolam by LC-MS/MS: 10 ng/mL
- Oxazepam by LC-MS/MS: 10 ng/mL
- Temazepam by LC-MS/MS: 10 ng/mL
- Clobazam by LC-MS/MS: 10 ng/mL
BNZU
608255

Benzodiazepines Confirmation, Random, Urine

Clinical Information: Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the drugs most commonly prescribed in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents.

Useful For: Detecting drug use involving benzodiazepines such as alprazolam, chlordiazepoxide, clonazepam, diazepam, midazolam, oxazepam, temazepam, clobazam, flunitrazepam, flurazepam, lorazepam, prazepam, triazolam, and zolpidem

Interpretation: Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: Alprazolam Alpha-hydroxyalprazolam (metabolite of alprazolam) Chlordiazepoxide Clonazepam 7-Aminoclonazepam (metabolite of clonazepam) Diazepam (separate prescribable drug and metabolite of medazepam) Nordiazepam (metabolite of clorazepate, halazepam, prazepam, diazepam and medazepam) Midazolam Alpha-hydroxy midazolam (metabolite of midazolam) Oxazepam (separate prescribable drug and metabolite of clorazepate, halazepam, prazepam, medazepam, temazepam, and diazepam) Temazepam (separate prescribable drug and metabolite of medazepam and diazepam) Clobazam N-Desmethylclobazam (metabolite of clobazam) Flunitrazepam 7-Aminoflunitrazepam (metabolite of flunitrazepam) Flurazepam 2-Hydroxy ethyl flurazepam (metabolite of flurazepam) Lorazepam Prazepam Triazolam Alpha-hydroxy triazolam (metabolite of triazolam) Zolpidem Zolpidem phenyl-4-carboxylic acid (metabolite of zolpidem)

The clearance half-life of long-acting benzodiazepines is more than 24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5 to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Clinic Laboratories Drugs of Abuse Testing Guide at www.mayocliniclabs.com/test-info/drug-book/index.html for additional information including metabolism, clearance (half-life), and approximate detection times.

Reference Values:

Cutoff concentrations:
Alprazolam by LC-MS/MS: 10 ng/mL
Alpha-Hydroxyalprazolam by LC-MS/MS: 10 ng/mL
Chlordiazepoxide by LC-MS/MS: 10 ng/mL
Clonazepam by LC-MS/MS: 10 ng/mL
7-Aminoclonazepam by LC-MS/MS: 10 ng/mL
Diazepam by LC-MS/MS: 10 ng/mL
Nordiazepam by LC-MS/MS: 10 ng/mL
Midazolam by LC-MS/MS: 10 ng/mL
Alpha-Hydroxy Midazolam by LC-MS/MS: 10 ng/mL
Oxazepam by LC-MS/MS: 10 ng/mL
Temazepam by LC-MS/MS: 10 ng/mL
Clobazam by LC-MS/MS: 10 ng/mL
N-Desmethyliclobazam by LC-MS/MS: 10 ng/mL
Flunitrazepam by LC-MS/MS: 10 ng/mL
7-Aminoflunitrazepam by LC-MS/MS: 10 ng/mL
Flurazepam by LC-MS/MS: 10 ng/mL
2-Hydroxy Ethyl Flurazepam by LC-MS/MS: 10 ng/mL
Lorazepam by LC-MS/MS: 10 ng/mL
Prazepam by LC-MS/MS: 10 ng/mL
Triazolam by LC-MS/MS: 10 ng/mL
Alpha-Hydroxy Triazolam by LC-MS/MS: 10 ng/mL
Zolpidem by LC-MS/MS: 10 ng/mL
Zolpidem Phenyl-4-Carboxylic acid by LC-MS/MS: 10 ng/mL

**Clinical References:**

### FBENZ

**Benztropine (Cogentin), Serum**

**Reference Values:**
Reference Range: 5.0 - 25.0 ng/mL

### BEREP

**Ber-EP4 (Epithelial Cell Adhesion Molecule/EPCAM)**

**Immunostain, Technical Component Only**

**Clinical Information:** Epithelial cell adhesion molecule/EPCAM (Ber-EP4) is expressed on most epithelial cells of the body, with the exception of squamous epithelium and mesothelium. It has been used to distinguish basal cell carcinoma from squamous cell carcinoma of the skin, and to distinguish pulmonary adenocarcinoma from mesothelioma.

**Useful For:** Aids in distinguishing basal cell carcinoma from squamous cell carcinoma of the skin
Aids in distinguishing pulmonary adenocarcinoma from mesothelioma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant...
quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**BBEET 82838 Berlin Beetle, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Berlin beetle Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

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

**Reference Values:**

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<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


**BERG 82892 Bermuda Grass, IgE, Serum**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 348
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Bermuda grass. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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

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Reference values apply to all ages.


**FBERY**

**Beryllium, Blood**

**Reference Values:**

Reference Range: <1.0 ng/mL

**BETV2**

**BET v2 (Profilin), IgE, Serum**

**Clinical Information:** Immunoglobulin E antibodies to the Bet v 2a profilin protein have been reported in 10% to 38% of birch pollen-allergic patients. Birch pollen is highly allergenic and is a significant cause of immediate hypersensitivity, affecting as much as 5% to 50% of the population of Western Europe. The presence of antibodies to Bet v 2, may also indicate sensitivity to other profilin containing pollens including ragweed pollen, mugwort pollen, and timothy grass pollen. The profilin Bet v2 is related to, and cross-reactive with, antibodies to the potential peanut allergen profilin Ara h5.
As profilin proteins are present in many other foods, sensitivity to profilin Bet v2 may be associated in broad allergen cross-reactivity among foods, including mango, peach, apple, hazelnut, celery, carrot, paprika, anise, fennel, coriander, cumin, tomato, and potato. The most common manifestation of allergy to food in profilin related allergic individuals is oral allergy syndrome. Profilins are generally not resistant to heat and digestion. Individuals with birch pollen allergy and oral allergy syndrome are more frequently allergic to apples and peaches than to other foods. In cases of allergic reaction associated with oral allergy syndrome, rhinitis, itching, tingling, and other mild reactions on the oropharyngeal mucosa were reported to be the most common complaints.

**Useful For:**
- Evaluation of patients suspected birch pollen allergy
- Evaluation of patients with suspected peanut allergy
- Evaluation of patients with oral allergy syndrome to other pollens or plant-based foods

**Interpretation:** Profilins are potentially cross-reactive allergenic proteins found in many plant pollens and tissues. IgE antibodies to the profilin Bet v2, while associated with birch pollen sensitivity, also represent a minor peanut allergen marker as it is cross-reactive with the peanut profilin Ara h5. The presence of antibodies to profilin Bet v2 is typically associated with milder allergic reactions and oral allergy syndrome.

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<tr>
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<td></td>
<td>Negative</td>
</tr>
<tr>
<td>0/1</td>
<td>0.10-0.34</td>
<td>Borderline/Equivocal</td>
</tr>
<tr>
<td>1</td>
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Concentrations > or =0.70 kU/L (Class 2 and above) will flag as abnormally high.

**Clinical References:**
electrophoresis and red blood cell indices. The majority of beta-globin chain variants are clinically and hematologically benign; however, some have important clinical consequences, such as erythrocytosis, cyanosis/hypoxia, chronic hemolysis, or unexplained microcytosis. Most of the common clinically significant hemoglobin (Hb) variants (ie, HbS, HbC, HbE, and others) are easily distinguished by hemoglobin electrophoresis and do not require molecular analysis. In addition, they are frequently found in complex hemoglobin disorders due to multiple genetic variants, and accurate classification requires sequencing data within the context of protein data. In some instances, beta-globin sequencing is necessary to identify or confirm the identity of rare variants, especially those associated with erythrocytosis and chronic hemolytic anemia. Rare hyper-unstable variants (also termed dominant beta thalassemia mutations) result in hemolytic anemia and do not create protein stable enough to be detectable by protein methods, including stability studies. They are not always associated with elevated HbA2 or microcytosis and, therefore, can be electrophoretically silent. These require a high degree of clinical suspicion as all electrophoretic testing as well as stability studies cannot exclude this condition. Beta thalassemia is an autosomal recessive condition characterized by decreased or absent synthesis of beta-globin chains due to sequence variants in the beta-globin gene (HBB). No abnormal protein is present and diagnosis by electrophoresis relies on hemoglobin fraction percentage alterations (ie, HbA2 or HbF elevations). Beta thalassemia can be split into 3 broad classes (categorized by clinical features): 1. Beta thalassemia trait (also called beta thalassemia minor and beta thalassemia carrier) (B[A]B[+] or B[A]B[0]) 2. Beta thalassemia intermedia (B[+]?B[+] or B[+]?B[0]) 3. Beta thalassemia major (B[+]?B[0] or B[0]?B[0]) Beta thalassemia trait is typically a harmless condition with varying degrees of microcytosis and hypochromia and sometimes mild anemia. Transfusions are not required. Beta thalassemia intermedia is a clinical distinction and is characterized by a more severe degree of anemia than beta thalassemia trait with few or intermittent transfusions required. Later in life, these individuals are at risk for iron overload even in the absence of chronic transfusion due to increased intestinal absorption of iron. Beta thalassemia major typically comes to medical attention early in life due to severe anemia, hepatosplenomegaly, and failure to thrive. Skeletal changes are also common due to expansion of the bone marrow. Without appropriate treatment these patients have a shortened lifespan. The majority of beta thalassemia variations (>90%) are point alterations, small deletions, or insertions, which are detected by beta-globin gene sequencing. The remaining beta thalassemia sequence variants are either due to large genomic deletions of HBB or, very rarely, trans-acting beta thalassemia variations located outside of the beta-globin gene cluster. Some rare beta-chain variants can be clinically or electrophoretically indistinguishable from beta thalassemia and cannot be confirmed without molecular analysis.

**Useful For:** Diagnosis of beta thalassemia intermedia or major Identification of a specific beta thalassemia sequence variant (ie, unusually severe beta thalassemia trait) Evaluation of an abnormal hemoglobin electrophoresis identifying a rare beta-globin variant Evaluation of chronic hemolytic anemia of unknown etiology Evaluation of hereditary erythrocytosis with left-shifted p50 oxygen dissociation results Preconception screening when there is a concern for a beta-hemoglobin disorder based on family history

**Interpretation:** The alteration will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

**Reference Values:**
An interpretive report will be provided.

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

AB2GP
Beta-2 Glycoprotein 1 Antibodies, IgA, Serum

Clinical Information: Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta-2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 antibodies that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta-2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms notably thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta-2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta-2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as "beta-2 GP1 antibodies." Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met.(4) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS, but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta-2GP 1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(5) Anticardiolipin and beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgA antibodies

Interpretation: Strongly positive results for IgG and IgM beta-2 glycoprotein 1 (beta-2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta-2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta-2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA beta-2 GP1 antibody result >15 U/mL with negative IgG and IgM beta-2 GP1 antibody results are not diagnostic for APS. Detection of beta-2 GP1 antibodies is not affected by anticoagulant treatment.

Reference Values:
Current as of June 14, 2021 12:13 pm CDT     800-533-1710 or 507-266-5700 or mayocliniclabs.com
<15.0 U/mL (negative)
15.0-39.9 U/mL (weakly positive)
40.0-79.9 U/mL (positive)
> or =80.0 U/mL (strongly positive)

Results are expressed in arbitrary units.
Reference values apply to all ages.


Beta-2 Glycoprotein 1 Antibodies, IgG and IgM, Serum

Clinical Information: Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta-2 GP1 and phospholipids in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 (beta-2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta-2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms, notably, thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta-2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Beta-2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as beta-2 GP1 antibodies. Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criterion and 1 laboratory criterion be met.(4) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta-2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(5) Anticardiolipin and beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of
beta-2 glycoprotein 1 (beta-2 GP1) IgG and IgM antibodies

**Interpretation:** Strongly positive results for beta-2 glycoprotein 1 (beta-2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta-2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta-2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta-2 GP1 antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <15.0 U/mL (negative)
- 15.0-39.9 U/mL (weakly positive)
- 40.0-79.9 U/mL (positive)
- > or =80.0 U/mL (strongly positive)

Results are expressed in arbitrary units and apply to IgG and IgM values. Reference values apply to all ages.

**Clinical References:**

**GB2GP**

**Beta-2 Glycoprotein 1 Antibodies, IgG, Serum**

**Clinical Information:** Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each. Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies. Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 antibodies that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms notably thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta-2 GP1 are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so-called direct assays) are referred to simply as "beta-2 GP1 antibodies." Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS.
but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >MPL, or >99th percentile), and/or the presence of IgG and/or IgM beta GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta-2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(5) Anticardiolipin and beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgG antibodies

**Interpretation:** Strongly positive results for beta 2 glycoprotein 1 (beta 2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM beta 2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta 2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta 2 GP1 antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <15.0 U/mL (negative)
- 15.0-39.9 U/mL (weakly positive)
- 40.0-79.9 U/mL (positive)
- > or =80.0 U/mL (strongly positive)

Results are expressed in arbitrary units.

Reference values apply to all ages.

**Clinical References:**

**Beta-2 Glycoprotein 1 Antibodies, IgM, Serum**

**Clinical Information:** Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 (beta-2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms, notably, thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta-2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as...
"beta-2 GP1 antibodies." Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met.(4) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta 2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(5) Anticardiolipin and beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgM antibodies

**Interpretation:** Strongly positive results for beta-2 glycoprotein 1 (beta-2 GPl) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta-2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta-2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta-2 GP1 antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <15.0 U/mL (negative)
- 15.0-39.9 U/mL (weakly positive)
- 40.0-79.9 U/mL (positive)
- > or =80.0 U/mL (strongly positive)

Results are expressed in arbitrary units. Reference values apply to all ages.


**B2MU**

**Beta-2 Microglobulin, Random, Urine**

**Clinical Information:** Beta-2 microglobulin is a low-molecular-weight protein that forms the light chain component of class I histocompatibility (HLA: human leukocyte antigen) antigens. Increased urine levels are seen in proximal tubular renal damage due to a variety of causes, including cadmium, mercury, lithium, or aminoglycoside toxicity; pyelonephritis; and Balkan nephropathy, a chronic interstitial nephritis of unknown etiology.

**Useful For:** Evaluation of renal tubular damage Monitoring exposure to cadmium and mercury

**Interpretation:** Increased excretion is consistent with renal tubular damage. Beta-2 microglobulin excretion is increased 100 to 1000 times normal levels in cadmium-exposed workers.

**Reference Values:**
- < or =300 mcg/L

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 356
**Beta-2 Transferrin: Detection of Spinal Fluid in Other Body Fluid**

**Clinical Information:** The diagnosis of cerebrospinal fluid (CSF) rhinorrhea or otorrhea (leakage of CSF into the nose or ear canal, usually as a result of head trauma, tumor, congenital malformation, or surgery) is often difficult to confirm. Traditional chemical analyses (eg, glucose, protein, specific gravity) are unreliable. Radiographic studies, especially those involving the injection of dyes or radiographic compounds, are costly and may introduce additional risks to the patient. Transferrin that migrates in the beta-1 electrophoretic fraction (beta-1 transferrin) is found in most body fluids. Beta-2 transferrin is a CSF-specific variant of transferrin and is used as an endogenous marker of CSF leakage. Beta-2 transferrin is formed by loss of sialic acid due to the presence of neuraminidase in the central nervous system. Beta-2 transferrin has also been called CSF-specific transferrin and tau protein. Prompt diagnosis and localization facilitates appropriate decisions and decreases the risk of meningitis.

**Useful For:** Detection of spinal fluid in body fluids, such as ear or nasal fluid

**Interpretation:** The cerebrospinal fluid (CSF) variant of transferrin is identified by its unique electrophoretic migration. If beta-1 and beta-2 transferrin are detected in drainage fluids, the specimen is presumed to be contaminated with CSF. The presence of beta-2 transferrin band is detectable with as little as 2.5% spinal fluid contamination of body fluid.

**Reference Values:**
Negative, no beta-2 transferrin (spinal fluid) detected

**Clinical References:**

**Beta-2-Microglobulin (Beta-2-M), Spinal Fluid**

**Clinical Information:** Beta-2-microglobulin (BETA-2-M) is a small membrane protein (11,800 Dalton) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows BETA-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Increased BETA-2-M levels in the cerebrospinal fluid (CSF) have been shown to be of diagnostic use in non-Hodgkin lymphoma with central nervous system involvement. Elevated CSF:serum ratios seen in patients with aseptic meningo-encephalitis suggest the possibility of neurologic processes including those associated with HIV infection and acute lymphoblastic leukemia. BETA-2-M measurement in multiple sclerosis seems to be of indeterminate usefulness.

**Useful For:** Evaluation of central nervous system inflammation and B-cell proliferative diseases

**Interpretation:** Elevations of cerebrospinal fluid beta-2-microglobulin levels may be seen in a number of diseases including malignancies, autoimmune disease, and neurological disorders.

**Reference Values:**
0.70-1.80 mcg/mL

**Clinical References:**

**B2M** 9234

**Beta-2-Microglobulin, Serum**

**Clinical Information:** Beta-2-microglobulin (beta-2-M) is a small membrane protein (11,800 Dalton) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows beta-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Serum beta-2-M levels are elevated in diseases associated with increased cell turnover. Levels are also elevated in several benign conditions such as chronic inflammation, liver disease, renal dysfunction, some acute viral infections, and a number of malignancies, especially hematologic malignancies associated with the B-lymphocyte lineage. In multiple myeloma, beta-2-M is a powerful prognostic factor and values <4 mcg/mL are considered a good prognostic factor. In renal tubular disease, serum levels are low and urine levels are high. Although urine beta-2-M has been used to assess tubular dysfunction, it is not stable in urine below pH 5.5. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Prognosis assessment of multiple myeloma Evaluation of renal tubular disorders

**Interpretation:** Serum beta-2-microglobulin (beta-2-M) <4 mcg/mL is a good prognostic factor in patients with multiple myeloma. In a study of pretreatment serum beta-2-M levels in 100 patients with myeloma it was reported that the median survival of patients with values >4 mcg/mL was 12 months, whereas median survival for patients with values <4 mcg/mL was 43 months.

**Reference Values:**
1.21-2.70 mcg/mL


**BAMY** 70634

**Beta-Amyloid Immunostain, Technical Component Only**

**Clinical Information:** Beta amyloid is a component of senile and diffuse plaques and neurofibrillary
tangles, a characteristic of Alzheimer disease. Beta amyloid is also a component of vascular amyloid in
the brain of dementia patients.

Useful For: Identification of senile plaques in neurodegenerative disease

Interpretation: This test does not include pathologist interpretation; only technical performance of
the stain is performed. If an interpretation is required order PATHC / Pathology Consultation for a full
diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as
showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a
control tissue is not included on the slide, a scanned image of the relevant quality control tissue is
available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the
context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hubin E, Van Nuland NA, Broersen K, Pauwels K: Transient dynamics of
Bloom GS: Amyloid-beta and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA

CTNNB

Beta-Catenin (CTNNB1) Mutation Analysis, Tumor
Clinical Information: Desmoid-type fibromatosis is a locally invasive soft tissue tumor. The
histological diagnosis of desmoid-type fibromatosis is challenging. Mutations in exon 3 of the
beta-catenin (BCAT also known as CTNNB1) gene have been identified in 50% to 87% of
desmoid-type fibromatosis, including T41A (121 A->G), S45P (133 T->C), and S45F (134 C->T), but
not in other soft tissue tumors. Patients harboring beta-catenin mutations may have a higher recurrence
rate compared to the patients with wild-type beta-catenin. Next-generation sequencing has recently
emerged as an accurate, cost-effective method to identify alterations across numerous genes. This test
uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic
mutations in the beta-catenin gene known to be associated with desmoid-type fibromatosis. The results
of this test can be useful for supporting a diagnosis of desmoid-type fibromatosis and predicting
prognosis.

Useful For: Distinguishing desmoid-type fibromatosis from other soft tissue tumors by assessing
gene targets with in the BCAT (CTNNB1) gene This test is not useful for hematological malignancies.

Interpretation: An interpretive report will be provided.

Reference Values:  
An interpretative report will be provided.

beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol
in paraffin-embedded sporadic desmoid-type fibromatosis by mutation-specific restriction enzyme

BCATN

Beta-Catenin Immunostain, Technical Component Only
Clinical Information: Beta-catenin is involved in cellular cohesion through binding to the
cytoplasmic tail of E-cadherin, and in intracellular signaling as a component of the Wnt pathway. In
normal cells, B-catenin levels are regulated by the adenomatous polyposis coli (APC) protein, which
promotes normal degradation of the protein. Alterations in either B-catenin or APC can result in
accumulation of the protein and abnormal localization in the nucleus. In the nucleus, B-catenin acts as a
cofactor in the upregulation of oncogenes including cyclin D1 and cmyc. In normal tissues, staining for
B-catenin is limited to the membrane. Aberrant nuclear staining can be used diagnostically in selected
tumors of the soft tissue (fibromatoses, endometrial stromal sarcoma), pancreas, liver and lung.

**Useful For:** Identification of aberrant nuclear staining pattern observed in some tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CTX 83175**

**Beta-CrossLaps, Serum**

**Clinical Information:** Human bone is continuously remodeled through a process of bone formation and resorption. Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is crosslinked at the N- and C-terminal ends of the molecule. During bone resorption, osteoclasts secrete a mixture of acid and neutral proteases that degrade the collagen fibrils into molecular fragments including C-terminal telopeptide (CTx). As bone ages, the alpha form of aspartic acid present in CTx converts to the beta form. Beta-CTx is released into the bloodstream during bone resorption and serves as a specific marker for the degradation of mature type I collagen. Elevated serum concentrations of beta-CTx have been reported in patients with increased bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and are of no diagnostic value. By contrast, bone turnover markers may be useful when the bone remodeling process is unbalanced. Abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia andrickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, and bone metastases, as well as various congenital diseases of bone formation and remodeling, can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption markers.

**Useful For:** Monitoring antiresorptive therapies (eg, bisphosphonates and hormone replacement therapy) in postmenopausal women treated for osteoporosis and individuals diagnosed with osteopenia An adjunct in the diagnosis of medical conditions associated with increased bone turnover

**Interpretation:** Elevated levels of beta-C-terminal telopeptide (CTx) indicate increased bone resorption. Increased levels are associated with osteoporosis, osteopenia, Paget disease, hyperthyroidism, and hyperparathyroidism. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy), a decrease of 25% or more from baseline beta-CTx levels (ie, prior to the start of therapy) 3 to 6 months after initiation of therapy indicates an adequate therapeutic response.

**Reference Values:**

Males
- <5 years: 242-1292 pg/mL
- 5-9 years: 351-1532 pg/mL
- 10-15 years: 447-2457 pg/mL
- 16-17 years: 478-1666 pg/mL
- 18-30 years: 120-946 pg/mL
- 31-50 years: 93-630 pg/mL
- 51-70 years: 35-836 pg/mL
>70 years: not established

Females

<5 years: 347-1508 pg/mL
5-9 years: 383-1556 pg/mL
10-15 years: 311-1776 pg/mL
16-17 years: 146-1266 pg/mL
Premenopausal: 25-573 pg/mL
Postmenopausal: 104-1008 pg/mL

Clinical References:

BGAW
60987

Beta-Galactosidase, Blood

Clinical Information:
Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the breakdown of gangliosides. Isolated deficiency of this enzyme is expressed clinically as 2 different autosomal recessive diseases, GM1 gangliosidosis and Morquio syndrome B (mucopolysaccharidosis IVB [MPS IVB] or Morquio B). Galactosialidosis (GS) is associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in protective protein cathepsin A (PPCA). Enzymatic testing is not reliable for carrier detection of these conditions. In GM1 gangliosidosis, reduced or absent beta-galactosidase activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months of age with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years old. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years of age presenting with developmental delays and a slower progression. Type 3 is an adult or chronic variant with onset between 3 and 30 years of age and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. In Morquio B, reduced or absent beta-galactosidase activity leads to the accumulation of glycosaminoglycans (GAG), particularly keratan sulfate, in lysosomes and interferes with normal functioning of cells, tissues, and organs. Morquio B typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Galactosialidosis is an autosomal recessive lysosomal storage disease caused by variants in the cathepsin A gene (CTSA) resulting in a combined deficiency of the enzymes beta-galactosidase and neuraminidase. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Typical clinical presentation includes coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal dysplasia, and early death, while the late infantile form is characterized by short stature, dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and/or heart valve problems. Individuals of Japanese ancestry make up the majority of patients with the juvenile/adult form of GS and typically develop symptoms after 4 years of age. These include neurologic degeneration, ataxia, and angiokeratomas. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or GS typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes or fibroblasts; however, additional testing and consideration of the patient's clinical findings are necessary to differentiate between these conditions. Follow-up testing may include LSDS / Lysosomal Storage Disorders Screen, Random, Urine, which
analyzes urine mucopolysaccharides, oligosaccharides, ceramide trihexosides, and sulfatides. The LSDS test can help differentiate between the 3 conditions to guide physicians in choosing the best confirmatory molecular testing option. See Lysosomal Storage Disorders Diagnostic Algorithm, Part 1 in Special Instructions.

**Useful For:** Diagnosis of GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis in whole blood specimens. This test is not useful for carrier detection.

**Interpretation:** Results below 5.0 nmol/hour/mL in properly submitted specimens are consistent with beta-galactosidase deficiency (GM1 gangliosidosis, Morquio syndrome B, or galactosialidosis). Further differentiation between GM1, Morquio syndrome B, and galactosialidosis is dependent on the patient's clinical findings and results of additional biochemical testing. Normal results (> or =5.0 nmol/h/mL) are not consistent with beta-galactosidase deficiency.

**Reference Values:**
> or =5.0 nmol/hour/mL

An interpretive report will be provided.

**Clinical References:**

**Beta-Galactosidase, Blood Spot**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the breakdown of gangliosides. The deficiency of this enzyme can be seen in the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. Enzymatic testing is not reliable for carrier detection of these conditions. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months of age with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years of age. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years of age, presenting with developmental delays, and a having a slower progression. Type 3 is an adult or chronic variant with onset between 3 and 30 years of age and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Mucopolysaccharidosis type IVB (MPS IVB or Morquio syndrome B) is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity leading to the accumulation of glycosaminoglycans (GAG), particularly keratan sulfate, in lysosomes and interferes with normal functioning of cells, tissues, and organs. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Galactosialidosis (GS) is an autosomal recessive lysosomal storage disease associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red
spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death, while the late infantile form is characterized by short stature, dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and heart valve problems. Individuals of Japanese ancestry makeup the majority of patients with the juvenile/adult form of GS and typically develop symptoms after 4 years of age. These include neurologic degeneration, ataxia, and angiokeratomas. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes or fibroblasts; however, additional testing and consideration of the patient's clinical findings are necessary to differentiate between these conditions. Follow-up testing may include LSDS / Lysosomal Storage Disorders Screen, Random, Urine, which analyzes urine mucopolysaccharides, oligosaccharides, ceramide trihexosides, and sulfatides. The LSDS test can help differentiate between the 3 conditions to guide physicians in choosing the best confirmatory molecular testing option. See Lysosomal Storage Disorders Diagnostic Algorithm, Part 1 in Special Instructions.

**Useful For:** Diagnosis of beta-galactosidase deficiency (GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis) in blood spot specimens This test is not useful for carrier detection.

**Interpretation:** Properly submitted specimens with results less than 5.0 nmol/h/mL are consistent with beta-galactosidase deficiency (GM1 gangliosidosis, Morquio syndrome B, or galactosialidosis). Further differentiation between GM1, Morquio syndrome B, and galactosialidosis is dependent on the patient's clinical findings and results of additional biochemical testing. Normal results (> or =5.0 nmol/hour/mL) are not consistent with beta-galactosidase deficiency.

**Reference Values:**
> or =5.0 nmol/hour/mL

An interpretive report will be provided.

**Clinical References:**

**Beta-Galactosidase, Leukocytes**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. Isolated deficiency of this enzyme is expressed clinically as 2 different diseases, GM1 gangliosidosis and Morquio syndrome B. Galactosialidosis is also associated with a deficiency of beta-galactosidase but in conjunction with neuraminidase secondary to a defect in protective protein cathepsin A (CTSA). Enzymatic testing is not reliable for carrier detection of these conditions. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years, presenting with developmental delays or regression and a slower clinical course. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to
200,000 live births. In mucopolysaccharidosis type IVB (MPS IVB, Morquio B), reduced or absent beta-galactosidase activity leads to the accumulation of glycosaminoglycans (GAG) in lysosomes and interferes with normal functioning of cells, tissues, and organs. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, and cardiac disease but no neurological involvement. Galactosialidosis is an autosomal recessive lysosomal storage disease (LSD) caused by variants in the cathepsin A gene (CTSA) resulting in a combined deficiency of the enzymes beta-galactosidase and neuraminidase. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Typical clinical presentation includes coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal dysplasia, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features, hepatosplenomegaly, and/or heart valve problems. The majority of individuals with the juvenile/adult form of GS are of Japanese ancestry and develop symptoms after 4 years of age, which include neurologic degeneration, ataxia, and angiokeratomas. Patients with mucolipidosis II/III (I-cell disease) may also demonstrate deficiency of beta-galactosidase in leukocytes, in addition to deficiency of other hydrolases. I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylgalcosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of beta-galactosidase activity is not the preferred diagnostic test for I-cell disease but may be included in the testing strategy. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes or fibroblasts; however, additional testing and consideration of the patient's clinical findings are necessary to differentiate between these conditions. Follow-up testing may include LSDS / Lysosomal Storage Disorders Screen, Random, Urine, which analyzes mucopolysaccharides, oligosaccharides, ceramide trihexosides, and sulfatides to help differentiate between the 3 conditions and guide physicians in choosing the best confirmatory molecular testing option.

**Useful For:** Aiding in the diagnosis of GM1 gangliosidosis, Morquio B disease, and galactosialidosis

This test is not suitable for carrier detection.

**Interpretation:** Very-low enzyme activity levels are consistent with GM1 gangliosidosis and Morquio B disease. Clinical findings must be used to differentiate between those 2 diseases. The deficiency of beta-galactosidase combined with neuraminidase deficiency is characteristic of galactosialidosis.

**Reference Values:**

> or =1.56 nmol/min/mg

**Clinical References:**


thalassemia, gamma-delta-beta thalassemia, and epsilon-gamma-delta-beta thalassemia, also result from functional loss of genes or the locus control region (LCR) that controls globin gene expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta-globin cluster locus. Most, but not all, of the large deletion beta-globin cluster disorders are associated with variably elevated hemoglobin (Hb) F percentages that persist after 2 years of age. In addition, most manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume (MCV) values. The correct classification of these deletions is important as they confer variable predicted phenotypes and some are more protective than others when found in combination with a second beta-globin variant, such as HbS or beta thalassemia. In addition, identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha thalassemia molecular results.

Useful For: Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH) or delta-beta thalassemia; Diagnosing less common causes of beta-thalassemia; these large deletional beta thalassemia alterations result in elevated hemoglobin (Hb) A2 and usually have slightly elevated HbF levels; Distinguishing homozygous HbS disease from a compound heterozygous HbS/large beta-globin cluster deletion disorder (ie, HbS/beta zero thalassemia, HbS/delta beta zero thalassemia, HbS/HPFH, HbS/gamma-delta-beta-thalassemia); Diagnosing complex thalassemias where the beta-globin gene and 1 or more of the other genes in the beta-globin cluster have been deleted; Evaluating and classifying unexplained increased HbF percentages; Evaluating microcytic neonatal anemia; Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha thalassemia; testing/normal Hb A2 percentages; Confirming gene fusion hemoglobin variants such as Hb Lepore and Hb P-Nilotic; Confirming homozygosity vs hemizygosity of alterations in the beta-like genes (HBB, HBD, HBG1, HBG2); This test is not useful for diagnosis or confirmation of alpha thalassemia, the most common beta thalassemias, or hemoglobin variants. It also does not detect nondeletional hereditary persistence of fetal hemoglobin.

Interpretation: The alterations will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

Reference Values: Only orderable as a reflex. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

An interpretive report will be provided.

expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta-globin cluster locus. Most, but not all, of the large deletion beta-globin cluster disorders are associated with variably elevated hemoglobin F percentages that persist after 2 years of age. In addition, most manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume (MCV) values. The correct classification of these deletions is important as they confer variable predicted phenotypes and some are more protective than others when found in combination with a second beta-globin variant, such as HbS or beta thalassemia. In addition, identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha thalassemia molecular results.

**Useful For:**
- Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH) or delta-beta thalassemia
- Diagnosing less common causes of beta thalassemia; these large deletional beta thalassemia variants result in elevated hemoglobin (Hb) A2 and usually have slightly elevated HbF levels
- Distinguishing homozygous Hb S disease from a compound heterozygous HbS/large beta-globin cluster deletion disorder (ie, HbS/beta zero thalassemia, Hb S/delta-beta zero thalassemia, HbS/HPFH, HbS/gamma-delta-beta thalassemia)
- Diagnosing complex thalassemias where the beta-globin gene and one or more of the other genes in the beta-globin cluster have been deleted
- Evaluating and classifying unexplained increased HbF percentages
- Evaluating microcytic neonatal anemia
- Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha thalassemia testing/normal HbA2 percentages
- Confirming gene fusion hemoglobin variants such as Hb Lepore and Hb P-Nilotic
- Confirming homozygosity vs hemizygosity of variants in the beta-like genes (HBB, HBD, HBG1, HBG2)

**Interpretation:** The alterations will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Beta-Globin Gene Sequencing, Blood**

**Clinical Information:** Beta-globin gene sequencing is useful in the evaluation of beta-globin chain variants and beta thalassemia. It detects almost all beta-globin variants and the most common beta thalassemia sequence variants, although prevalence is ethnicity dependent. Because these conditions are often complex, this test should always be interpreted in the context of protein studies, such as hemoglobin electrophoresis and red blood cell indices. The majority of beta-globin chain variants are clinically and hematologically benign; however, some have important clinical consequences, such as erythrocytosis, cyanosis/hypoxia, chronic hemolysis, or unexplained microcytosis. Most of the common clinically significant hemoglobin (Hb) variants (ie, HbS, HbC, HbE, and others) are easily distinguished by hemoglobin electrophoresis and do not require molecular analysis. In addition, they are frequently found in complex hemoglobin disorders due to multiple genetic variants, and accurate classification requires sequencing data within the context of protein data. In some instances, beta-globin sequencing is necessary to identify or confirm the identity of rare variants, especially those associated with erythrocytosis and chronic hemolytic anemia. Rare hyper-unstable variants (also termed dominant beta thalassemia mutations) result in hemolytic anemia and do not create protein stable enough to be detectable by protein methods, including stability studies. They are not always associated with elevated HbA2 or microcytosis.
and, therefore, can be electrophoretically silent. These require a high degree of clinical suspicion as all electrophoretic testing as well as stability studies cannot exclude this condition. Beta thalassemia is an autosomal recessive condition characterized by decreased or absent synthesis of beta-globin chains due to alterations in the beta-globin gene (HBB). No abnormal protein is present and diagnosis by electrophoresis relies on hemoglobin fraction percentage alterations (ie, HbA2 or HbF elevations). Beta-thalassemia can be split into 3 broad classes (categorized by clinical features): 1. Beta thalassemia trait (also called beta thalassemia minor and beta thalassemia carrier) (B[A]B[+] or B[A]B[0]). 2. Beta thalassemia intermedia (B[+]B[+] or B[+]B[0]). 3. Beta thalassemia major (B[+]B[0] or B[0]B[0]) Beta thalassemia trait is typically a harmless condition with varying degrees of microcytosis and hypochromia and sometimes mild anemia. Transfusions are not required. Beta thalassemia intermedia is a clinical distinction and is characterized by a more severe degree of anemia than beta thalassemia trait with few or intermittent transfusions required. Later in life, these individuals are at risk for iron overload even in the absence of chronic transfusion due to increased intestinal absorption of iron. Beta thalassemia major typically comes to medical attention early in life due to severe anemia, hepatosplenomegaly, and failure to thrive. Skeletal changes are also common due to expansion of the bone marrow. Without appropriate treatment these patients have a shortened lifespan. The majority of beta thalassemia variations (>90%) are point alterations, small deletions, or insertions, which are detected by beta-globin gene sequencing. The remaining beta thalassemia sequence variants are either due to large genomic deletions of HBB or, very rarely, trans-acting beta thalassemia variations located outside of the beta-globin gene cluster. Some rare beta-chain variants can be clinically or electrophoretically indistinguishable from beta thalassemia and cannot be confirmed without molecular analysis.

**Useful For:** Evaluates for the following in an algorithmic process for the HAEV1 / Hemolytic Anemia Evaluation, Blood; HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood; MEV1 / Methemoglobinemia Evaluation, Blood; REVE1 / Erythrocytosis Evaluation, Whole Blood; THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum: -Diagnosis of beta thalassemia intermedia or major -Identification of a specific beta thalassemia sequence variant (ie, unusually severe beta thalassemia trait) -Evaluation of an abnormal hemoglobin electrophoresis identifying a rare beta-globin variant -Evaluation of chronic hemolytic anemia of unknown etiology -Evaluation of hereditary erythrocytosis with left-shifted p50 oxygen dissociation results -Preconception screening when there is a concern for a beta-hemoglobin disorder based on family history

**Interpretation:** The alteration will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

**Reference Values:**
Only orderable as a reflex. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

An interpretive report will be provided.

**Clinical References:**

**Beta-Glucosidase, Leukocytes**

**Clinical Information:** Gaucher disease is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid beta-glucosidase (glucocerebrosidase) enzyme activity. Absent or reduced
activity of this enzyme results in accumulation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosyl sphingosine) in the lysosomes and interferes with the normal functioning of cells. Clinical features and severity of symptoms are widely variable within Gaucher disease, but in general, the disorder is characterized by abnormal blood parameters such as decreased red blood cells (anemia) and/or platelets (thrombocytopenia), bone disease, and hepatosplenomegaly. Individuals with more severe types of Gaucher disease may have central nervous system (CNS) involvement. There are 3 clinical subtypes of the disorder that vary with respect to age of onset and clinical presentation. Type 1 is the most common type, representing 95% of all cases, and is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, and no CNS involvement. Type 2 typically has a very severe progression with onset in the first 2 years of life including neurologic disease, hepatosplenomegaly, and lung disease, with death usually between 2 and 4 years due to lung failure. Individuals with type 3 may have onset prior to 2 years of age, but the progression is not as severe, and they may survive into the third and fourth decade. Finally, there is a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Treatment is available in the form of enzyme replacement therapy (ERT), substrate reduction therapy, and chaperone therapy for types 1 and 3. Individuals with type 3 may benefit from bone marrow transplantation. The incidence of type 1 ranges from 1 in 20,000 to 200,000 in the general population, but it is much more frequent among Ashkenazi Jewish population with an incidence between 1 in 400 and 900. Types 2 and 3 both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of "Gaucher cells" on bone marrow examination. Significantly reduced or absent enzyme activity of acid beta-glucosidase is diagnostic. Additionally, the biomarker, glucopsychosine is elevated in symptomatic patients and supports a diagnosis of Gaucher disease (see GPSY / Glucopsychosine, Blood Spot; GPSYP / Glucopsychosine, Plasma; GPSYW / Glucopsychosine, Blood). A targeted variant panel may allow for detection of disease-causing variants in affected patients (GAUP / Gaucher Disease, Mutation Analysis, GBA, Varies). In addition, full sequencing of the GBA gene allows for detection of disease-causing variants in affected patients in whom a targeted variant panel identifies no variants or only a single variant (GBAZ / Gaucher Disease, Full Gene Analysis, Varies).

Useful For: Diagnosis of Gaucher disease This test is not intended for carrier detection.

Interpretation: Individuals affected with Gaucher disease will have enzyme levels less than 3.53 nmol/h/mg protein. In our experience some carriers will also have less than 3.53 nmol/h/mg protein activity.

Reference Values:
> or =3.53 nmol/hour/mg protein
  An interpretative report will be provided.

Note: Results from this assay do not reflect carrier status because of individual variation of beta-glucosidase enzyme levels.


BHCG 61718 Beta-Human Chorionic Gonadotropin, Quantitative, Serum

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Clinical Information: Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight: MW approximately 36,000 Dalton: Da) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyrotropin (previously known as thyroid-stimulating hormone: TSH). The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da, glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans) it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. hCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in particular seminomatous and nonseminomatous testicular tumors; ovarian germ cell tumors; gestational trophoblastic disease (GTD; hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including this assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours, and eventually return to the reference range.

Useful For: Monitoring patients for retained products of conception Aiding in the diagnosis of gestational trophoblastic disease (GTD), testicular tumors, ovarian germ cell tumors, teratomas, and, rarely, other human chorionic gonadotropin (hCG)-secreting tumors Serial measurement of hCG following treatment for: -Monitoring therapeutic response in GTD or in hCG-secreting tumors -Detecting persistent or recurrent GTD or hCG-secreting tumors This test is not intended to detect or monitor pregnancy.

Interpretation: After delivery, miscarriage, or pregnancy termination, human chorionic gonadotropin (hCG) falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. An absent or significantly slower decline is seen in patients with retained products of conception. Gestational trophoblastic disease (GTD) is associated with very considerable elevations of hCG, usually above 2 multiples of the medians for gestational age persisting or even rising beyond the first trimester. Serum hCG levels are elevated in approximately 40% to 50% of patients with nonseminomatous testicular cancer and 20% to 40% of patients with seminoma. Markedly elevated levels of hCG (>5000 IU/L) are uncommon in patients with pure seminoma and indicate the presence of a mixed testicular cancer. Ovarian germ cell tumors (approximately 10% of ovarian tumors) display elevated hCG levels in 20% to 50% of cases. Teratomas in children may overproduce hCG, even when benign, resulting in precocious pseudopuberty. Levels may be elevated to similar levels as seen in testicular cancer. Among nonreproductive tumors, hepatobiliary tumors (hepatoblastomas, hepatocellular carcinomas, and cholangiocarcinomas) and neuroendocrine tumors (eg, islet cell tumors and carcinoids) are those most commonly associated with hCG production. Many hCG-producing tumors also produce other embryonic proteins or antigens, in particular alpha fetoprotein (AFP). AFP should, therefore, also be measured in the diagnostic workup of such neoplasms. Complete therapeutic response in hCG-secreting tumors is characterized by a decline in hCG levels with an apparent half-life of 24 to 36 hours and eventual return to concentrations within the reference range. GTD and some tumors may produce hyperglycosylated hCG with a longer half-life, but an apparent half-life of more than 3 days suggests the presence of residual hCG-producing tumor tissue. A rise in hCG levels above the reference range in patients with hCG-producing tumors that had previously been treated successfully, suggests possible local or distant metastatic recurrence.

Reference Values:
Children(1,2)
**BHSF 8877**

**Beta-Human Chorionic Gonadotropin, Quantitative, Spinal Fluid**

**Clinical Information:** Human chorionic gonadotropin (hCG) is synthesized during pregnancy by syncytiotrophoblast cells. hCG may also be produced by neoplastic cells of testicular tumors (seminomas or nonseminomas), ovarian germ cell tumors, gestational trophoblastic disease, choriocarcinoma and various nontrophoblastic tumors including breast, ovarian, pancreatic, cervical, gastric, and hepatic cancers. Measurement of hCG is used as an adjunct in the diagnosis of germ cell tumors. The presence of hCG in cerebrospinal fluid (CSF) is suggestive of tumor presence. Pure germinomas are associated with low hCG concentrations in both serum and CSF. A subset of nongerminomatous germ cell tumors contains syncytiotrophoblastic giant cells. These tumors are associated with moderately increased hCG concentrations (<1,000 IU/L) in the serum and/or CSF, and the survival rate in patients suffering these tumors is worse than that of patients with pure germinomas. In contrast, choriocarcinomas, another subset of nongerminomatous germ cell tumors, are associated with very high hCG concentrations (>1,000 IU/L) in both serum and CSF. Quantification of the hCG in CSF can be important in guiding treatment and monitoring response to treatment of these tumors. The combination of the specific antibodies used in the Roche Beta HCG immunoassay recognize the holo-hormone, "nicked" forms of hCG, the beta-core fragment, and the free beta-subunit.

**Useful For:** Aiding in the diagnosis of brain metastases of testicular cancer or extragonadal intracerebral germ cell tumors

**Interpretation:** Elevated levels of human chorionic gonadotropin in spinal fluid indicate the probable presence of central nervous system metastases or recurrence of tumors in patients with germ cell tumors.
including patients with testicular cancer or choriocarcinoma.

**Reference Values:**
<1.0 IU/L

**Clinical References:**

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**BHYD**

**Beta-Hydroxybutyrate, Serum**

**Clinical Information:** Beta-hydroxybutyrate (BHB) is 1 of 3 sources of ketone bodies. Its relative proportion in the blood (78%) is greater than the other 2 ketone bodies, acetoacetate (20%) and acetone (2%). During carbohydrate deprivation (starvation, digestive disturbances, frequent vomiting), decreased carbohydrate utilization (diabetes mellitus), glycogen storage diseases, and alkalosis, acetoacetate production increases. The increase may exceed the metabolic capacity of the peripheral tissues. As acetoacetate accumulates in the blood, a small amount is converted to acetone by spontaneous decarboxylation. The remaining and greater portion of acetoacetate is converted to BHB.

**Useful For:** Monitoring therapy for diabetic ketoacidosis. Investigating the differential diagnosis of any patient presenting to the emergency room with hypoglycemia, acidosis, suspected alcohol ingestion, or an unexplained increase in the anion gap. In pediatric patients, the presence or absence of ketonemia/uria is an essential component in the differential diagnosis of inborn errors of metabolism. Serum beta-hydroxybutyrate is a key parameter monitored during controlled 24-hour fasts.

**Interpretation:** The beta-hydroxybutyrate (BHB)/acetoacetate ratio is typically between 3:1 and 7:1 in severe ketotic states. Serum BHB increases in response to fasting, but should not exceed 0.4 mmol/L following an overnight fast (up to 12 hours). In pediatric patients, a hypo- or hyper-ketotic state (with or without hypoglycemia) may suggest specific groups of metabolic disorders.

**Reference Values:**
<0.4 mmol/L

**Clinical References:**

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**BLACT**

**Beta-Lactamase**

**Clinical Information:** Various bacteria produce a class of enzymes called beta-lactamases, which may be mediated by genes on plasmids or chromosomes. Production of beta-lactamase may be constitutive or induced by exposure to antimicrobials. Beta-lactamases hydrolyze (and thereby inactivate) the beta-lactam rings of a variety of susceptible penicillins and cephalosporins. Beta-lactamases are classified by their preferred antimicrobial substrate and the effect of various inhibitors (such as clavulanic acid) on them. Some antimicrobials, such as cefazolin and cloxacillin are resistant to such hydrolysis (at least for staphylococcal beta-lactamases). Beta-lactamase producing strains of the following are resistant to many types of penicillin: Staphylococcus species, Hemophilus influenzae, Neisseria gonorrhoeae, Bacteroides species, Enterococcus species, and Moraxella catarrhalis. The above organisms, when isolated from critical specimens such as blood or spinal fluid, should always be tested for beta-lactamase production. Addition of a beta-lactamase inhibitor to a
beta-lactam (such as sulbactam plus ampicillin) restores the activity of the antimicrobials.

**Useful For:** Predicting the resistance of beta-lactamase producing isolates to hydrolysis-susceptible beta-lactam antimicrobials

**Interpretation:** A positive test indicates production of beta-lactamase.

**Reference Values:**
Negative (reported as positive or negative)


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**Beta-Lactoglobulin, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to beta-lactoglobulin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Bicarbonate, Serum**

**Clinical Information:** Bicarbonate is the second largest fraction of the anions in plasma. Included in this fraction are the bicarbonate (HCO$_3^-$) and carbonate (CO$_3^{2-}$) ions, carbon dioxide in physical solution, as well as the carbamino compounds. At the physiological pH of blood, the concentration of carbonate is 1/1000 that of bicarbonate. The carbamino compounds are also present in such low quantities that they are generally not mentioned specifically. The bicarbonate content of serum or plasma is a significant indicator of electrolyte dispersion and anion deficit. Together with pH determination, bicarbonate measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with acid-base imbalance in the respiratory and metabolic systems. Some of these conditions are diarrhea, renal tubular acidosis, carbonic anhydrase inhibitors, hyperkalemic acidosis, renal failure, and ketoacidosis.

**Useful For:** Diagnosis and treatment of acid-base imbalance in respiratory and metabolic systems

**Interpretation:** Alterations of bicarbonate (HCO$_3^-$) and carbon dioxide (CO$_2$) dissolved in plasma are characteristic of acid-base imbalance. The nature of the imbalance cannot, however, be inferred from the bicarbonate value itself, and the determination of bicarbonate is rarely ordered alone. Its value has significance in the context of other electrolytes determined with it and in screening for electrolyte imbalance.

**Reference Values:**

- **Males**
  - 12-24 months: 17-25 mmol/L
  - 3 years: 18-26 mmol/L
  - 4-5 years: 19-27 mmol/L
  - 6-7 years: 20-28 mmol/L
  - 8-17 years: 21-29 mmol/L
  - ≥ 18 years: 22-29 mmol/L

- **Females**
  - 1-3 years: 18-25 mmol/L
  - 4-5 years: 19-26 mmol/L
  - 6-7 years: 20-27 mmol/L
  - 8-9 years: 21-28 mmol/L
  - ≥ 10 years: 22-29 mmol/L

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


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**Bicarbonate, Urine**

**Reference Values:** Reporting limit determined each analysis.

- Normally: None Detected

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**Bile Acid Profile, Serum**

**Clinical Information:** Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic
clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. The concentration of bile acids in serum is influenced by many different liver diseases due to the inability of the liver to efficiently extract circulating bile acids from portal blood. In addition, bile acid levels are altered in several biochemical genetic conditions, such as peroxisomal biogenesis disorders like Zellweger syndrome and disorders of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl-CoA racemase deficiency, due to the loss of specific enzymes important for bile acid metabolism. This analysis includes a quantitative characterization of primary and secondary bile acids as well as 2 bile acid precursor species for the assessment of bile acid metabolism.

Useful For: Evaluating the enterohepatic cycle consisting of the biliary system, intestine, portal circulation, and hepatocytes Supporting researchers in need of free and conjugated values of all 20 bile acid species as well as total bile acid

Interpretation: Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum C27 bile acids are seen in patients with peroxisomal biogenesis disorders such as Zellweger syndrome or single enzyme defects of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl CoA racemases. Totals of the free and conjugated bile acid species for all 20 bile acids in addition to total bile acids will be reported. No interpretive report will be provided.

Reference Values:
Chenodeoxycholic acid: < or =2.26 nmol/mL Cholic acid: < or =2.74 nmol/mL Deoxycholic acid: < or =2.84 nmol/mL Dihydroxycholestanoic acid: < or =0.07 nmol/mL Glycochenodeoxycholic acid: < or =5.14 nmol/mL Glycocholic acid: < or =2.17 nmol/mL Glycodeoxycholic acid: < or =3.88 nmol/mL Glycohyodeoxycholic acid: < or =0.01 nmol/mL Glycolithocholic acid: < or =0.11 nmol/mL Glycoursodeoxycholic acid: < or =1.00 nmol/mL Hyodeoxycholic acid: < or =0.12 nmol/mL Lithocholic acid: < or =0.09 nmol/mL Taurochenodeoxycholic acid: < or =0.80 nmol/mL Taurocholic acid: < or =0.31 nmol/mL Taurodeoxycholic acid: < or =0.78 nmol/mL Taurohyodeoxycholic acid: < or =0.02 nmol/mL Taurolithocholic acid: < or =0.04 nmol/mL Tauroursodeoxycholic acid: < or =0.05 nmol/mL Trihydroxycholestanoic acid: < or =1.73 nmol/mL Ursodeoxycholic acid: < or =0.64 nmol/mL Total bile acids: < or =19.00 nmol/mL

malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. This bile acid test for peroxisomal disorders measures concentrations of C27 bile acids, which are diagnostic markers for peroxisomal biogenesis disorders such as Zellweger syndrome and single enzyme defects of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl-CoA racemase deficiency. Elevated levels of C27 bile acids may enable diagnosis of peroxisomal biogenesis disorders and bile acid synthesis defects in children with liver cholestasis. Treatment for peroxisomal biogenesis disorders and bile acid synthesis defects with cholic acid is available. Measurement of C27 bile acids before and during treatment with bile acid therapy such as cholic acid can assist with monitoring of treatment efficacy.

**Useful For:** Biomarker for peroxisomal biogenesis disorders such as Zellweger syndrome and single enzyme defects of bile acid synthesis including D-bifunctional protein deficiency and alpha methyl CoA racemases Monitoring patients receiving bile acid therapy such as cholic acid for liver disease due to peroxisomal biogenesis disorders or single enzyme defects in bile acid synthesis

**Interpretation:** Increases in serum C27 bile acids are seen in patients with peroxisomal biogenesis disorders such as Zellweger syndrome or single enzyme defects of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl CoA racemases. Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. The values of 2 bile acid precursors, dihydroxycholestanolic acid and trihydroxycholestanolic acid, will be reported, along with total cholic acid, total chenodeoxycholic acid, total ursodeoxycholic acid, and total bile acids. No interpretive report will be provided.

**Reference Values:**
- Dihydroxycholestanolic acid ≤ 0.10
- Trihydroxycholestanolic acid ≤ 1.30
- Total cholic acid ≤ 5.00
- Total chenodeoxycholic acid ≤ 6.00
- Total ursodeoxycholic acid ≤ 2.00
- Total bile acids ≤ 19.00

**Clinical References:**

**Clinical Information:** Bile acids are natural products of cholesterol synthesis that aid in the emulsification and absorption of dietary fats in the small intestine. The majority of bile acids are reabsorbed in the ileum of the healthy individual, with only 5% excreted in feces.(1) Primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are deconjugated and dehydroxylated via intestinal bacteria into secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively.(2) The sum of CA, CDCA, DCA, LCA, and ursodeoxycholic acid (UDCA) compose the majority of bile acids in the feces. Impaired absorption of bile acids in the terminal ileum leads to excess bile acids in the colon that can cause diarrhea from chloride and water secretion; a condition called bile acid malabsorption (BAM). Irritable bowel syndrome (IBS) is a nonspecific multifactorial
disorder involving the large intestine. IBS is characterized by cramping, bloating, diarrhea, and constipation and classified as either IBS-D (diarrhea) or IBS-C (constipation) by the Rome III criteria.(3) Up to 50% of IBS-D patients have accelerated colonic transit time; the mechanism of IBS-D pathophysiology is varied with more than 25% having BAM.(1,4) Several methods have been developed for detection of BAM, but are not widely available in clinical practice.(5) Therefore, patients are often placed on trials of bile acids sequestrants to determine if symptoms improve. Quantitation of fecal bile acids aids in screening for IBS-D and identification of patients with chronic diarrhea who may benefit from bile acid sequestrant therapy.

Useful For: Aids to evaluate patients suspected of having irritable bowel syndrome-diarrhea (IBS-D) symptoms due to bile acid malabsorption

Interpretation: Elevated total fecal bile acid or percent cholic acid plus chenodeoxycholic acid is consistent with the diagnosis of bile acid malabsorption. Pharmacological treatment with bile acid sequestrants has been shown to improve symptoms in some patients.

Reference Values:
> or = to 18 years:
  - Sum of cholic acid and chenodeoxycholic acid < or =9.7%
  - Total bile acids < or =2619 mcmoles/48 hours

Reference values have not been established for patients who are <18 years of age

Clinical References:

Bile Acids, Fractionated and Total, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations.

Useful For: Measuring tauro- and glycol-conjugated and unconjugated bile acid concentrations in serum Monitoring patients receiving bile acid therapy, such as cholic acid, deoxycholic acid, or ursodeoxycholic acid Aiding in the evaluation of liver function; evaluation of liver function changes before the formation of more advanced clinical signs of illness such as icterus Determining hepatic dysfunction as a result of chemical and environmental injury Indicating hepatic histological improvement in chronic hepatitis C
Bile Acids, Total, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. Significant increases in total bile acids in nonfasting pregnant females can aid in the diagnosis of cholestasis. Other factors, such as complete medical history, physical exam, and liver function tests should also be considered.

Useful For: An aid in the evaluation of liver function Evaluation of liver function changes before the formation of more advanced clinical signs of illness such as icterus An aid in the determination of hepatic dysfunction as a result of chemical and environmental injury An indicator of hepatic histological improvement in chronic hepatitis C patients responding to interferon treatment An indicator for intrahepatic cholestasis of pregnancy

Interpretation: Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum bile acids are seen in patients with acute hepatitis, chronic hepatitis, liver sclerosis, liver cancer, and intrahepatic cholestasis of pregnancy.

Reference Values: < or =10 mc mol/L

Reference interval applies to fasting total bile acid concentrations.


FBAC 75012

Bile Acids, Urine

Clinical Information: Diagnostic testing in pediatric and adult patients presenting with conditions of cholestatic liver disease, neurological disease, or fat-soluble vitamin malabsorption of unknown etiology. Urine FAB-MS analysis provides a rapid and cost-effective means of diagnosing the most common of the genetic defects in the metabolism of cholesterol to the primary bile acids. Mass spectrometry testing may be used to monitor the biochemical response to primary bile acid therapy and to help in decisions on dose adjustments, where compliance should lead to a reduction in levels of atypical bile acids.

BILAO 71917

Biliary Tract Malignancy, FISH, Varies

Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (e.g., aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for malignancy

Interpretation: An interpretive report will be provided.

Reference Values:
No abnormality detected by fluorescence in situ hybridization


FBILM 70587

Biliary Tract Malignancy-Cytology, FISH, Varies

Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (e.g., aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for malignancy

Interpretation: An interpretive report will be provided. A positive cytology diagnosis is normally
definitive for the presence of malignancy. Suspicious or atypical results need further confirmation by clinical observation, repeat cytology, or perhaps appropriate biopsy.

**Reference Values:**
Negative for malignancy.

**Clinical References:**

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**Bilirubin Direct, Serum**

**Clinical Information:** Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin while the remaining 15% is produced from the RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. Direct bilirubin is a measurement of conjugated bilirubin. Jaundice can occur as a result of problems at each step in the metabolic pathway. Disorders may be classified as those due to: increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). Inherited disorders in which direct bilirubinemia occurs include Dubin-Johnson syndrome and Rotor syndrome. Jaundice of the newborn where direct bilirubin is elevated includes idiopathic neonatal hepatitis and biliary atresia. The most commonly occurring form of jaundice of the newborn, physiological jaundice, results in unconjugated (indirect) hyperbilirubinemia. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The increased production of bilirubin that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatocellular diseases such as hepatitis and space-occupying lesions of the liver, and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Evaluation of jaundice and liver functions

**Interpretation:** Direct bilirubin levels must be assessed in conjunction with total and indirect levels and the clinical setting.

**Reference Values:**
> or =12 months: 0.0-0.3 mg/dL

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

**Clinical References:**

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**Bilirubin, Amniotic Fluid**

**Clinical Information:** The presence of bilirubin in amniotic fluid, which results in a yellow color, is an indicator of fetal erythroblastosis. Visual inspection of amniotic fluid is unreliable because bilirubin is not the only cause of an excessive yellow color; therefore, the presence of bilirubin must be
confirmed with spectrophotometric methods. Meconium may contribute a green color (biliverdin) that can obscure the color of bilirubin and hemoglobin.

**Useful For:** Evaluation of Rh disease, ie, hemolytic disease of the fetus Monitoring disease progression to assess need for fetal transfusion

**Interpretation:** The reference range for bilirubin in amniotic fluid is related to the gestational age of the fetus. Refer to either the Queenan Curve (gestational age <27 weeks) or the Liley Chart (gestational age >27 weeks) listed under Interpretation of Amniotic Fluid Bilirubin Results (Delta OD 450) in Special Instructions.

**Reference Values:**
Interpretation of fetal risk is dependent upon gestational age.
Refer to either the Queenan Curve (gestational age <27 weeks) or the Liley Chart (gestational age >27 weeks) listed under Interpretation of Amniotic Fluid Bilirubin Results (Delta OD 450) in Special Instructions.

**Clinical References:**

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**Bilirubin, Body Fluid**

**Clinical Information:** Peritoneal fluid: Bilirubin is typically measured in peritoneal fluid of patients with suspected bile duct leak or gallbladder perforation as a screening test prior to imaging or cholecsintigraphy. If the value is higher than that of serum and is greater than 6 mg/dL, and the ascitic fluid amylase is not elevated (indicating upper intestinal perforation), it can be assumed that the gallbladder has perforated into the peritoneum (choleperitoneum) and/or bowel or biliary perforation has occurred.(1) Furthermore, biliary leakage after laparoscopic cholecystectomy is the most common post-operative complication.(2) While endoscopy is a beneficial first-line treatment for the management of bile leaks there often are logistical issues which hinder the procedure from being performed rapidly. Post-cholecystectomy patients generally have a drain in place (particularly a Jackson Pratt or JP drain) and may undergo bilirubin testing on the drain fluid as an objective assessment of a bile leak. A body fluid/serum bilirubin ratio of greater than 5 in a JP drain fluid is highly sensitive and specific for bile leak.(3) Pleural fluid: Measurement of bilirubin in pleural fluid has been investigated to aid in the differentiation of transudative and exudative effusions in pursuit of more specific biomarkers than traditional light criteria measuring total protein and lactate dehydrogenase. Bilirubin values tend to be higher in exudates than in transudates, although there is some overlap between groups which limits the usefulness of its measure.(4) Other fluids: Determination of body fluid bilirubin concentration can aid in the distinction between a transudative and an exudative fluid or identify the presence of bile in other fluid compartments.

**Useful For:** Evaluation of peritoneal fluid or abdominal drain fluid as a screening test for bile leakage May aid in the distinction between a transudative and an exudative pleural effusion

**Interpretation:** Bilirubin may be measured in other fluids although the decision limits are not well defined in fluids other than pleural fluid. Fluid to serum bilirubin ratios are expected to be less than or equal to 1.0 and should be interpreted in conjunction with other clinical findings.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Bilirubin, Random, Urine

Clinical Information: Bilirubin is primarily derived from metabolism of hemoglobin. Only conjugated bilirubin is excreted into the urine and normally only trace amounts can be detected in urine. Elevated urinary bilirubin occurs in patients with obstructive jaundice or jaundice due to hepatocellular disease or injury. However, urine bilirubin is relatively insensitive for detection of liver disease. Hyperbilirubinemia due to hemolysis is principally due to unconjugated bilirubin, and therefore does not result in increased urinary bilirubin.

Useful For: Limited use in screening of patients for liver disease

Interpretation: Elevated urinary bilirubin is suggestive of hepatocellular disease or post-hepatic biliary obstruction.

Reference Values: Negative


Bilirubin, Serum

Clinical Information: Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute
therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

**Reference Values:**

Direct Bilirubin

> or =12 months: 0.0-0.3 mg/dL

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

Total Bilirubin

0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.

7-14 days: <15.0 mg/dL

15 days to 17 years: < or =1.0 mg/dL

> or =18 years: < or =1.2 mg/dL


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**Bilirubin, Total, Serum**

**Clinical Information:** Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from the red blood cell precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is a frequent and direct result of these disturbances. Jaundice can occur as a result of problems at each step in the metabolic pathway. Disorders may be classified as those due to: increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

**Interpretation:** The level of bilirubinemia that results in kernicterus in a given infant is unknown. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number
of factors including TSB, age, clinical history, physical examination and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

**Reference Values:**
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: <15.0 mg/dL
15 days to 17 years: < or =1.0 mg/dL
> or =18 years: < or =1.2 mg/dL

**Clinical References:**

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**Biogen Program, Alzheimer Disease Evaluation, Spinal Fluid**

**Clinical Information:** Currently the diagnosis of probable Alzheimer disease (AD) is made based on clinical symptoms, largely by the exclusion of other causes of dementia, with postmortem evidence of AD pathology required to confirm the diagnosis. Two common neuropathologic features found in the brain of patients with AD dementia are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. These 2 groups of molecules are the most established biomarkers of the disease used in clinical and research practice. Positron emission tomography (PET) imaging using FDA-approved amyloid radiotracer to visualize the presence of amyloid lesions in the cerebral cortex is available in some specialized centers. Measuring Abeta peptides and Tau proteins in cerebrospinal fluid (CSF) is being proposed as an alternative/adjunct to imaging studies to assess AD pathology. Recently the use of these biomarkers has been included in the new consensus research diagnostic criteria for AD, mild cognitive impairment (MCI), and preclinical AD, proposed by the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework. The CSF assays included in this evaluation are beta-amyloid (1-42; Abeta42), total-Tau (t-Tau) and phosphorylated-Tau (p-Tau). Abeta42 is approximately 4 kDa protein of 42 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein (APP). Due to its hydrophobic nature, Abeta42 has the propensity to form aggregates and oligomers. Oligomers form fibrils that accumulate into amyloid plaques. These pathological changes in Abeta42 are reflected by the decrease in the CSF concentrations of Abeta42 and/or by the increase in the brain uptake of specific tracers during beta-amyloid PET. Tau is present as 6 isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-mRNA. The t-Tau assay measures all these isoforms. The most common post-translational modification of Tau proteins is phosphorylation. During neurodegeneration, abnormal phosphorylation leads to the formation of intracellular neurofibrillary tangles composed of the Tau protein that has undergone hyperphosphorylation and developed aggregates of hyper-phosphorylated Tau proteins called p-Tau. The p-Tau assay detects p-Tau at threonine 181 (p-Tau 181). Pathological changes associated with AD are reflected by an increase in the CSF concentrations of t-Tau and p-Tau. Increases in CSF t-Tau reflect the intensity of the neuronal and axonal damage and degeneration and is associated with a faster progression from MCI to AD. Increases in CSF p-Tau concentrations are also associated with a faster progression from MCI to AD with more rapid cognitive decline in AD patients and in mild AD dementia cases. The Alzheimer's Association has developed an appropriate use criterion (AUC), in order to guide safe and optimal use of CSF testing for AD pathology detection in the diagnostic process. The use of CSF biomarker testing may be indicated for the following patient groups: 1) patients with subjective cognitive decline (SCD) who are considered to be at increased risk for AD; 2) patients with MCI that is persistent, progressing, and unexplained; 3) patients with symptoms that suggest possible AD; 4) MCI or dementia with an onset at an early age (less than 65); 5) patients
meeting core clinical criteria for probable AD with typical age of onset; 6) patients whose dominant symptom is a change in behavior (eg, Capgras syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression) and where AD diagnosis is being considered. Ultimately, the decision to initiate CSF testing for the evaluation of suspected AD is also based on the clinical judgment of expert providers and the patient's individual presentation.

**Useful For:** Assessment of adults with cognitive impairment being evaluated for Alzheimer disease and other causes of cognitive impairment. Biogen’s Amyloid Beta Confirmed Program: This test should not be used to predict the development of dementia or other neurologic conditions or to monitor response to therapies.

**Interpretation:** A beta-amyloid (1-42; Abeta42) result greater than 1026 pg/mL is consistent with a negative amyloid positron emission tomography (PET) scan. A negative amyloid PET scan indicates the presence of no or sparse neuritic plaques and is inconsistent with a neuropathological diagnosis of Alzheimer disease (AD). An Abeta42 result greater than 1026 pg/mL is associated with a reduced likelihood that a patient's cognitive impairment is due to AD. Total Tau (t-Tau) and phosphorylated Tau (p-Tau) cerebrospinal fluid (CSF) concentrations increase approximately 2 to 3-times as much in patients with mild-moderate AD compared to age-matched controls. A t-Tau and/or p-Tau concentration of less than or equal to 238 pg/mL and less than or equal to 21.7 pg/mL, respectively, reduces the likelihood that a patient's cognitive impairment is due to AD. The use of p-Tau/Abeta42 ratio provides better concordance with amyloid PET scan when compared to Abeta42, p-Tau and t-Tau individually. A cut-off of 0.023 provides optimal balance between NPA (negative % agreement) and PPA (positive % agreement) when compared to amyloid PET results. A p-Tau/Abeta42 ratio of less than or equal to 0.023 has a 92% NPA with normal amyloid PET. A ratio of greater than 0.023 has a 92% PPA with abnormal amyloid PET. High CSF t-Tau protein concentrations are found in other neurodegenerative diseases such as prion disease or Creutzfeldt-Jakob disease (CJD). In this situation, an elevated t-Tau concentration and an increased t-Tau to p-Tau ratio has a very high specificity for differential diagnoses of CJD. Abnormal (+)/Normal (-) Individual comments for AD reporting values Abeta42 (-) Phosphorylated-Tau (-) Total-Tau (-) Normal concentrations of Abeta42, phosphorylated-Tau (p-Tau), and total-Tau (t-Tau) concentrations are present in CSF. These results are not consistent with the presence of pathological changes associated with Alzheimer's disease. Abeta42 (+) p-Tau (-) t-Tau (-) Abnormal Abeta42 concentrations are present in CSF. P-Tau and t-Tau concentrations are normal. These results may consistent with Alzheimer's related pathologic change. Abeta42 (-) p-Tau (+) t-Tau (-) Abnormal Abeta42 and p-Tau concentrations are present in CSF. The t-Tau concentration is normal. These results are consistent with the presence of Alzheimer's disease. Abeta42 (-) p-Tau (+) t-Tau (+) Abnormal Abeta42, p-Tau and t-Tau concentrations are present in CSF. These results are consistent with the presence of Alzheimer's disease. Abeta42 (+) p-Tau (-) t-Tau (+) Abnormal Abeta42 and t-Tau concentrations are present in CSF. The p-Tau concentration is normal. These results may be consistent with Alzheimer's related pathologic change. Abeta42 (-) p-Tau (+) t-Tau (-) Abnormal p-Tau concentrations are present in CSF. Abeta42 and t-Tau concentrations are normal. These results are not consistent with the presence of pathological changes associated with Alzheimer's disease. Abeta42 (-) p-tau (-) t-Tau (+) Abnormal t-Tau concentrations are present in CSF. The Abeta42 and p-Tau concentrations are normal. These results are not consistent with the presence of pathological changes associated with Alzheimer's disease. Abeta42 (-) p-Tau (+) t-Tau (+) Abnormal p-Tau and t-Tau concentrations are present in CSF. The Abeta42 concentration is normal. These results are not consistent with the presence of pathological changes associated with Alzheimer's disease. This table and interpretations are based on the NIA-AA Research Framework diagnostic recommendations.(1)

**Reference Values:**

Beta-amyloid (1-42) (Abeta42): >1026 pg/mL

Total-Tau: < or =238 pg/mL

Phosphorylated-Tau (p-Tau) 181: < or =21.7 pg/mL

p-Tau/Abeta42: < or =0.023


**Biotin, Serum**

**Clinical Information:** Biotin is a water soluble B complex vitamin (vitamin B7 or vitamin H) that is an essential cofactor for the synthesis of fatty acids, catabolism of branched chained amino acids, and for gluconeogenesis. It is usually found at relatively low endogenous concentrations in patients on a normal diet. However, biotin can be found in over-the-counter multi-vitamins, prenatal vitamins, and dietary supplements marketed for hair, skin, and nail growth. Additionally, treatment of certain progressive multiple sclerosis patients with high doses of biotin has been reported to be beneficial. Biotin supplementation from either over-the-counter or prescription sources can result in extremely elevated circulating biotin. Some immunoassays in the clinical laboratory use chemistry that utilizes the high affinity and avidity that biotin has for binding avidin (or streptavidin). As a result, high serum biotin concentrations can yield inaccurate laboratory results in laboratory assays that utilize this biotin-streptavidin chemistry. Specifically, specimens with high biotin can yield falsely decreased results when the testing methodology utilizes sandwich-based methods or falsely increased results when the methodology utilizes competitive binding methods. Each clinical laboratory method that utilizes biotin-streptavidin chemistry has a defined biotin concentration limit above which serum biotin can interfere with assay results. This test measures free biotin concentrations in serum and can be used to determine whether a patient has high biotin concentrations that are likely from biotin supplementation/treatment.

**Useful For:** Measurement of biotin in serum Assessment of biotin concentrations in individuals taking biotin supplements Investigation of unexpected results from immunoassays that utilize biotin-streptavidin detection methods This test is not useful as a screen for biotinidase deficiency.

**Interpretation:** Biotin results that are significantly higher than the reference interval indicate biotin supplementation.

**Reference Values:**

For ages 18 years or older: <0.3 ng/mL

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


**Biotinidase Deficiency, BTD Full Gene Analysis, Varies**

**Clinical Information:** Biotinidase deficiency is an inherited metabolic disease caused by reduced levels of biotinidase, an enzyme that recycles biotin by releasing it from its metabolic product, biocytin,
or exogenous dietary proteins. Biotin is a vitamin that serves as a coenzyme for 4 carboxylases that are essential for amino acid catabolism, gluconeogenesis, and fatty acid synthesis. Depletion of free biotin reduces carboxylase activity, resulting in secondary carboxylase deficiency. Depending on the amount of residual biotinidase activity, individuals can have either profound or partial biotinidase deficiency. Age of onset and clinical phenotype vary among individuals. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. Untreated profound biotinidase deficiency (<10% of normal biotinidase activity) manifests within the first decade of life as seizures, hypotonia, neurosensory hearing loss, respiratory problems, and cutaneous symptoms including skin rash, alopecia, and recurrent viral or fungal infections. Among children and adolescents with profound biotinidase deficiency, clinical features include ataxia, sensorineural hearing loss, developmental delay, and eye problems such as optic neuropathy leading to blindness. Partial biotinidase deficiency (10%-30% of normal biotinidase activity) is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement. Treatment with biotin has been successful in both preventing and reversing the clinical features associated with biotinidase deficiency. As a result, biotinidase deficiency is included in most newborn screening programs in order to prevent disease. Biotinidase deficiency exhibits a similar clinical presentation to carboxylase and holocarboxylase synthetase deficiency. Therefore, measurement of the biotinidase enzyme is required to differentiate between these diseases and ensure proper diagnosis. Newborn screening for biotinidase deficiency involves direct analysis of the biotinidase enzyme from blood spots obtained shortly after birth. This enables early identification of potentially affected individuals and quick follow-up with confirmatory biochemical and molecular testing. Biotinidase deficiency is inherited in an autosomal recessive manner, caused by mutations in the biotinidase gene (BTD). The carrier frequency for biotinidase deficiency in the general population is about 1:120. Several common mutations in the BTD gene have been identified, accounting for about 60% of affected individuals. Sequencing of the entire BTD gene detects other, less common, disease-causing mutations. While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency. The recommended first-tier test to screen for biotinidase deficiency is a biochemical test that measures biotinidase enzyme activity, either newborn screening or BIOTS / Biotinidase, Serum. Molecular tests form the basis of confirmatory or carrier testing. Individuals with decreased enzyme activity are more likely to have 2 identifiable mutations in the BTD gene by molecular genetic testing.

**Useful For:** Second-tier test for confirming biotinidase deficiency (indicated by biochemical testing or newborn screening) Carrier testing of individuals with a family history of biotinidase deficiency, but disease-causing mutations have not been identified in an affected individual

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Clinical Information: Biotinidase deficiency is an autosomal recessive disorder caused by variants in the biotinidase gene (BTD). Age of onset and clinical phenotype vary among individuals depending on the amount of residual biotinidase activity. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. The carrier frequency for biotinidase deficiency within the general population is about 1 in 120. Untreated profound biotinidase deficiency typically manifests within the first decade of life as seizures, ataxia, developmental delay, hypotonia, sensorineural hearing loss, vision problems, skin rash, and alopecia. Partial biotinidase deficiency is associated with a milder clinical presentation, and may include cutaneous symptoms without neurologic involvement. Certain organic acidurias, such as holocarboxylase synthase deficiency, isolated carboxylase synthase deficiency, and 3-methylcrotonylglycinuria, present similarly to biotinidase deficiency. Serum biotinidase levels can help rule out these disorders. Treatment with biotin is successful in preventing the clinical features associated with biotinidase deficiency. In symptomatic patients, treatment will reverse many of the clinical features except developmental delay, vision, and hearing complications. As a result, biotinidase deficiency is included in most newborn screening programs. This enables early identification and treatment of presymptomatic patients. Molecular tests are useful for confirmatory or carrier testing. When biotinidase enzyme activity is deficient, sequencing of the entire BTD gene (BTDZ / Biotinidase Deficiency, BTD Full Gene Analysis, Varies) allows for detection of disease-causing variants in affected patients. Identification of familial variants allows for testing of at-risk family members (FMTT / Familial Mutation, Targeted Testing, Varies). While genotype-phenotype correlations are not well established, it appears that certain genetic variants are associated with profound biotinidase deficiency, while others are associated with partial deficiency.

Useful For: Preferred test for the diagnosis of biotinidase deficiency Follow-up testing for certain organic acidurias

Interpretation: The reference range is 3.5 U/L to 13.8 U/L. Partial deficiencies and carriers may occur at the low end of the reference range. Values below 3.5 U/L are occasionally seen in specimens from unaffected patients.

Reference Values:
3.5-13.8 U/L


FBFPI 57925

Bird Fancier's Precipitin Panel I

Reference Values:

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Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 387
The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

**Birt-Hogg-Dube Syndrome, FLCN Full Gene Analysis, Varies**

**Clinical Information:** The clinical characteristics of Birt-Hogg-Dube syndrome (BHDS) include cutaneous manifestations (fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons), pulmonary cysts/history of pneumothorax, and various types of renal tumors. Skin lesions typically appear during the third and fourth decades of life and typically increase in size and number with age. Lung cysts are mostly bilateral and multifocal; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax. Individuals with BHDS have an increased risk of renal tumors that are typically bilateral and multifocal and usually slow growing; median age of tumor diagnosis is 48 years with a range from 31 to 71 years. Some families have renal tumor and/or autosomal dominant spontaneous pneumothorax without cutaneous manifestations. BHDS is inherited in an autosomal dominant manner and penetrance is considered to be very high. FLCN (also known as folliculin or BHD) is the only gene known to be associated with BHDS. Sequence analysis detects mutations in FLCN in 88% of affected individuals. Recent studies have reported that multi-exonic deletions can account for up to 5% to 10% of additional mutations. (2, 3) Molecular genetic testing is indicated in all individuals known to have or suspected of having BHDS, including individuals with one of the following: -Five or more facial or truncal papules with at least 1 histologically confirmed fibrofolliculoma, with or without a family history of BHDS -Facial papules histologically confirmed to be angiofibroma in an individual who does not fit the clinical criteria of tuberous sclerosis complex (TSC) or multiple endocrine neoplasia type 1 (MEN1) -Multiple and bilateral chromophobe, oncocytic, and/or hybrid renal tumors -A single oncocytic, chromophobe, or oncocytic hybrid renal tumor and a family history of renal cancer with any of these renal cell tumor family history of renal cancer with any of the above renal cell tumor types -A family history of autosomal dominant primary spontaneous pneumothorax without a history of smoking or chronic obstructive pulmonary disease (COPD) In the absence of an increased risk of developing childhood malignancy, the American Society of Clinical Oncology (ASCO) recommends delaying genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing.

**Useful For:** Genetic diagnosis of Birt-Hogg-Dube syndrome for clinical management, risk assessment for related clinical symptoms, and genetic counseling for family members

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

**Reference Values:**

An interpretive report will be provided.

**Bismuth, Blood**

**Clinical Information:** Bismuth is used in the production of alloys, pigments, and chemical additives. Various compounds have also been used as therapeutic agents, astringents, antacids.(1) Bismuth subsalicylate (Pepto-Bismol) is one example commonly used for indigestion and diarrhea. In unexposed individuals, bismuth blood concentrations were typically less than 0.02 mcg/L compared to peptic ulcer patients taking bismuth medications where the concentrations ranged from 4 to 30 mcg/L.(2-4) Elimination from the body takes place primarily by the urinary and fecal routes, but the exact proportion contributed by each route is still unknown. Elimination from blood displays multicompartment pharmacokinetics with half-lives of 8 to 16 hours (early) and 5 to 11 days (late).(1) A number of toxic effects have been attributed to bismuth compounds in humans including: nephropathy, encephalopathy, osteoarthropathy, gingivitis, stomatitis, and colitis. Common early symptoms include salivation, mucosal swelling, discoloration of the tongue, gums, abdominal pain, and nausea.(1)

**Useful For:** Determining bismuth toxicity

**Interpretation:** Normal blood concentrations for unexposed individuals are less than 1 ng/mL and the therapeutic range is 4 to 30 ng/mL.(2-4)

**Reference Values:**
- <1 ng/mL (unexposed)
- 4-30 ng/mL (therapeutic)

**Clinical References:**
5. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018

**Bismuth, Serum**

**Reference Values:**
- Reference Range: <4.0 ng/mL
- Whole blood is the preferred specimen for assessment of Bismuth exposure.

**Bismuth, Urine**

**Reference Values:**
- Units: ng/mL
- Whole blood is the preferred specimen for assessment of Bismuth exposure.

**BK Virus, Molecular Detection, PCR, Plasma**

**Clinical Information:** Polyomaviruses are small (45 nm, approximately 5,000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance, Simian virus 40 (SV-40), JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years
of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients the average time from transplant to diagnosis is about 40 weeks (range 6-150).(3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) Viral loads of above 10,000 copies/mL in plasma may indicate a risk for BKVAN (see QBK / BK Virus, Molecular Detection, Quantitative, PCR, Plasma).

**Useful For:** Rapid detection of BK virus DNA

**Interpretation:** Results of plasma tests are reported in terms of the presence or absence of BK virus (BKV). Detection of BKV DNA in clinical specimens may support the clinical diagnosis of renal or urologic disease due to BKV. Correlation of qualitative results with clinical presentation and BK viral load in urine and/or plasma is recommended.

**Reference Values:**
Negative

**Clinical References:**

**BK Virus, Molecular Detection, PCR, Random, Urine**

**Clinical Information:** Polyomaviruses are small (45 nm, approximately 5,000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance; SV-40, JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by age 5 and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients the average time from transplant to diagnosis is about 40 weeks (range 6-150).(3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) However, BKV DNA is typically detectable in urine prior to plasma and may serve as an indication of impending BKVAN. Viral loads of above 100,000 copies/mL in urine may also indicate a risk for BKVAN (see QBKU / BK Virus, Molecular Detection, Quantitative, PCR, Urine).

**Useful For:** Rapid detection of BK virus DNA

**Interpretation:** Results of urine tests are reported in terms of the presence or absence of BK virus (BKV). Detection of BKV DNA in clinical specimens may support the clinical diagnosis of renal or urologic disease due to BKV. Correlation of qualitative results with clinical presentation and BK-viral
Reference Values:
Negative


BK Virus, Molecular Detection, Quantitative, PCR, Plasma

Clinical Information: Polyomaviruses are small (45 nm, approximately 5000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance: Simian virus 40 (SV-40), JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans. Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and BKV-associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients, the average time from transplant to diagnosis is about 40 weeks (range 6-150). Quantitative polymerase chain reaction analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy. The presence of BKV DNA in plasma at levels at or above 3200 IU/mL may correlate with an increased risk of BKVAN with this assay. Furthermore, the trend of viral DNA quantitation (eg, increasing, decreasing) may be helpful in predicting the onset of BKVAN. Serial monitoring of viral loads may be indicated to assess changing levels of BKV DNA.

Useful For: A prospective and diagnostic marker for the development of nephropathy in renal transplant recipients. This test should not be used to screen healthy patients. Depending on the population, varying percentages of patients may be found to be positive.

Interpretation: Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads above 3200 IU/mL BKV DNA in plasma may also indicate a risk for BKVAN. This assay does not cross react with other polyomaviruses, including JC virus and Simian virus 40 (SV-40)

Reference Values: None detected

BK Virus, Molecular Detection, Quantitative, PCR, Urine

Clinical Information: Polymaviruses are small (45 nm, approximately 5000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance; SV-40, JC virus (JCV) and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients, the average time from transplant to diagnosis is about 40 weeks (range 6-150).(3) Polymerase chain reaction analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) However, BKV DNA is typically detectable in urine prior to plasma and may serve as an indication of impending BKVAN. Viral loads of greater than 32,000 IU/mL in urine may also indicate a risk for BKVAN. Serial monitoring of viral loads may be indicated to assess changing levels of BKV DNA.

Useful For: A prospective and diagnostic marker for the development of BK virus nephropathy in renal transplant recipients. This test should not be used to screen healthy patients. Depending on the population, varying percentages of patients may be found to be positive.

Interpretation: Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads of above 32,000 IU/mL in urine may also indicate a risk for BKVAN. This assay does not cross react with other polymaviruses, including JC virus and SV-40.

Reference Values:
None detected

Black/White Pepper, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to black or white pepper Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
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</table>

sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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

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

**Reference Values:**

<table>
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<th>Class</th>
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<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Blastomyces Antibody Immunodiffusion, Serum**

**Clinical Information:** The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon.

**Useful For:** Detection of antibodies in serum specimens in patients with blastomycosis

**Interpretation:** A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Routine culture of clinical specimens (eg, respiratory specimen) is recommended in cases of suspected, active blastomycosis.

**Reference Values:**

Negative

**Blastomyces Antibody Immunodiffusion, Spinal Fluid**

**Clinical Information:** The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

**Useful For:** Detection of antibodies in spinal fluid specimens from patients with blastomycosis

**Interpretation:** A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production, or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

**Reference Values:**
Negative

**Clinical References:**

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**Blastomyces Antibody, Enzyme Immunoassay, Serum**

**Clinical Information:** Blastomyces dermatitidis, an adimorphic fungus, is endemic throughout the Midwestern, south-central, and southeastern United States, particularly in regions around the Ohio and Mississippi river valley, the Great Lakes and the Saint Lawrence River. It is also found in regions of Canada. Blastomyces is an environmental fungus, preferring moist soil and decomposing organic matter, which produces fungal spores that are released and inhaled by animals or humans. At body temperature, the spores mature into yeast, which can stay in the lungs or disseminate through the bloodstream to other parts of the body. Recently, through phylogenetic analysis, Blastomyces dermatitidis has been separated into two distinct species; B. dermatitidis and Blastomyces gilchristii, both able to cause blastomycosis in infected patients. Interestingly, B. dermatitidis infections are associated more frequently with dissemination, particularly in elderly patients, smokers and immunocompromised hosts, while B. gilchristii has primarily been associated with pulmonary and constitutional symptoms. Approximately 50% of patients infected with Blastomyces will develop symptoms, which are frequently non-specific and, include fever, cough, night sweats, myalgia or arthralgia, weight loss, chest pain and fatigue. Typically symptoms appear anywhere from 3 weeks to 3 months following infection. Diagnosis of blastomycosis relies on a combination of assays, including culture and molecular testing on appropriate specimens and serologic evaluation for both antibodies to and antigen released from Blastomyces. Although culture remains the gold standard method and is highly specific, the organism can take several days to weeks to grow, and sensitivity is diminished in cases of acute or localized disease. Similarly, molecular testing offers high specificity and a rapid turnaround time, however, sensitivity is imperfect. Detection of an antibody response to Blastomyces offers high specificity, however, results may be falsely negative in acutely infected patients and in immunosuppressed patients.

**Useful For:** Aiding in the diagnosis of blastomycosis

**Interpretation:** A positive result indicates that IgG and/or IgM antibodies to Blastomyces were detected. The presence of antibodies is presumptive evidence that the patient was or is currently infected with (or was exposed to) Blastomyces. A negative result indicates that antibodies to Blastomyces were not detected. The absence of antibodies is presumptive evidence that the patient was not infected with Blastomyces. However, the specimen may have been obtained before antibodies were detectable or the patient may be immunosuppressed. If infection is suspected, another specimen should be collected 7 to
14 days later and submitted for testing. Specimens testing positive or equivocal will be submitted for further testing by another conventional serologic test (eg, SBL / Blastomyces Antibody by Immunodiffusion, Serum).

**Reference Values:**
- Negative
- Reference values apply to all ages.

**BLEASTOMYCES ANTIGEN VALUE**

Not detected: 0.0 ng/mL
Detected: <1.3 ng/mL
Detected: 1.3-20.0 ng/mL
Detected: >20.0 ng/mL


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**ALBLD 603305**

**Bleeding Diathesis Profile, Limited, Plasma**

**Clinical Information:** Bleeding problems may be associated with a wide variety of coagulation abnormalities or may be due to problems not associated with coagulation (trauma and surgery as obvious examples). A partial listing of causes follows. -Deficiency or functional abnormality (congenital or acquired) of any of the following coagulation proteins: fibrinogen (factor I), factor II (prothrombin), factor V, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia C; bleeding severity not always proportionate to factor level), factor XIII (fibrin-stabilizing factor), von Willebrand factor (VWF antigen and activity), and alpha-2 plasmin inhibitor and plasminogen activator inhibitor (PAI-I; severe deficiency in rare cases). Neither alpha-2 plasmin inhibitor nor PAI-I are included as a routine bleeding diathesis assay component, but either can be performed if indicated or requested. -Deficiency (thrombocytopenia) or functional abnormality of platelets such as congenital (Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc) and acquired (myeloproliferative disorders, uremia, drugs, etc) disorders. Platelet function abnormalities cannot be studied on mailed-in specimens. -Specific factor inhibitors (most commonly directed against factor VIII); factor inhibitors occur in 10% to 15% of the hemophilia population and are more commonly associated with severe deficiencies of factor VIII or IX (antigen <1%). The inhibitor appears in response to transfusion therapy with factor concentrates with no correlation of occurrence and amount of therapy. Factor VIII inhibitors may occur spontaneously in the postpartum patient, with certain malignancies, in association with autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), in the elderly, and for no apparent reason. -Other acquired causes of increased bleeding include paraproteinemia; other factor-specific inhibitors, including those against factor V, factor XI; or virtually any of the coagulation proteins. -Acute disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), which is a fairly common cause of bleeding. Bleeding can also occur in patients with chronic ICF.

**Useful For:** Detection of the more common potential causes of abnormal bleeding (eg, factor deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors) and a simple screen to evaluate for an inhibitor or severe deficiency of factor XIII (rare) This test is not useful for assessing platelet function (eg, congenital or acquired disorders such as Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disease, myeloproliferative disease, associated platelet dysfunction), which requires fresh platelets

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


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**BTROP 82374**

**Blomia tropicalis, IgE, Serum**

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

**Useful For:** Aiding in the diagnosis of an allergic disease and defining the allergens responsible for eliciting signs and symptoms Identifying allergens that may be responsible for allergic disease and/or anaphylactic episode, confirming sensitization to particular allergens prior to beginning immunotherapy, and investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<td>2</td>
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<tr>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Blood Urea Nitrogen (BUN), Serum**

**Clinical Information:** Urea is the final degradation product of protein and amino acid metabolism. In protein catabolism, the proteins are broken down to amino acids and deaminated. The ammonia formed in this process is synthesized to urea in the liver. This is the most important catabolic pathway for eliminating excess nitrogen in the human body. Increased blood urea nitrogen (BUN) may be due to prerenal causes (cardiac decompensation, water depletion due to decreased intake and excessive loss, increased protein catabolism, and high protein diet), renal causes (acute glomerulonephritis, chronic nephritis, polycystic kidney disease, nephrosclerosis, and tubular necrosis), and postrenal causes (eg, all types of obstruction of the urinary tract, such as stones, enlarged prostate gland, tumors). The determination of serum BUN currently is the most widely used screening test for the evaluation of kidney function. The test is frequently requested along with the serum creatinine test since simultaneous determination of these 2 compounds appears to aid in the differential diagnosis of prerenal, renal and postrenal hyperuremia.

**Useful For:** Screening test for evaluation of kidney function
**Interpretation:** Serum blood urea nitrogen (BUN) determinations are considerably less sensitive than BUN clearance (and creatinine clearance) tests, and levels may not be abnormal until the BUN clearance has diminished to less than 50%. Clinicians frequently calculate a convenient relationship, the urea nitrogen:creatinine ratio—serum bun in mg/dL/serum creatinine in mg/dL. For a normal individual on a normal diet, the reference interval for the ratio ranges between 12 and 20, with most individuals being between 12 and 16. Significantly lower ratios denote acute tubular necrosis, low protein intake, starvation, or severe liver disease. High ratios with normal creatinine levels may be noted with catabolic states of tissue breakdown, prerenal azotemia, high protein intake, etc. High ratios associated with high creatinine concentrations may denote either postrenal obstruction or prerenal azotemia superimposed on renal disease. Because of the variability of both the BUN and creatinine assays, the ratio is only a rough guide to the nature of the underlying abnormality. Its magnitude is not tightly regulated in health or disease and should not be considered an exact quantity.

**Reference Values:**

**Males**
- 1-17 years: 7-20 mg/dL
- > or =18 years: 8-24 mg/dL

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

**Females**
- 1-17 years: 7-20 mg/dL
- > or =18 years: 6-21 mg/dL

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


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**Blood Worm, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to blood worm Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>

Current as of June 24, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 399
2 0.70-3.49 Positive  
3 3.50-17.4 Positive  
4 17.5-49.9 Strongly positive  
5 50.0-99.9 Strongly positive  
6 > or =100 Strongly positive Reference values apply to all ages.

### Clinical References

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**MUSS 82548**

**Blue Mussel, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to blue mussel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</table>

Blueberry IgG

Interpretation:

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

Blueberry, IgE, Serum

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

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

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

Reference Values:

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</tbody>
</table>

**BMPR1A Gene, Full Gene Analysis, Varies**

**Clinical Information:** Juvenile polyposis syndrome (JPS) is a rare hereditary cancer predisposition syndrome caused by alterations in the SMAD4 or BMPR1A genes. JPS is characterized by the presence of multiple histologically defined juvenile polyps in the upper and/or lower gastrointestinal (GI) tract and an increased risk for GI cancers. Age of onset for cancer development is typically in the second or third decade of life, although some patients present with a more severe infantile-onset form of the disease. JPS is inherited in an autosomal dominant fashion, although a significant proportion of probands have no family history. Approximately 50% of patients with JPS have an identifiable alteration in the SMAD4 or BMPR1A genes.

**Useful For:** Confirmation of juvenile polyposis syndrome for patients with clinical features

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

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**BOB1 Immunostain, Technical Component Only**

**Clinical Information:** BOB-1 is a transcriptional co-activator that interacts with the transcription factors OCT-1 or OCT-2 in regulating transcription of immunoglobulin genes. In normal tonsil, the germinal center B cells all express BOB-1, while only scattered cells in the mantle zone express this protein. Expression of BOB-1, OCT-2, and PU.1 transcription factors are often down-regulated in classic Hodgkin lymphomas, in contrast to many cases of diffuse large B-cell lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Bone Alkaline Phosphatase, Serum

Clinical Information: Bone alkaline phosphatase (BAP) is the bone-specific isoform of alkaline phosphatase. A glycoprotein that is found on the surface of osteoblasts, BAP reflects the biosynthetic activity of these bone-forming cells. BAP has been shown to be a sensitive and reliable indicator of bone metabolism. Normal bone is constantly undergoing remodeling in which bone degradation or resorption is balanced by bone formation. This process is necessary for maintaining bone health. If the process becomes uncoupled and the rate of resorption exceeds the rate of formation, the resulting bone loss can lead to osteoporosis and, consequently, a higher susceptibility to fractures. Osteoporosis is a metabolic bone disease characterized by low bone mass and abnormal bone microarchitecture. It can result from a number of clinical conditions including states of high bone turnover, endocrine disorders (primary and secondary hyperparathyroidism and thyrotoxicosis), osteomalacia, renal failure, gastrointestinal diseases, long-term corticosteroid therapy, multiple myeloma, and cancer metastatic to the bones. Paget disease is another common metabolic bone disease caused by excessive rates of bone remodeling resulting in local lesions of abnormal bone matrix. These lesions can result in fractures or neurological involvement. Antiresorptive therapies are used to restore the normal bone structure.

Useful For: Diagnosis and assessment of severity of metabolic bone disease including Paget disease, osteomalacia, and other states of high bone turnover Monitoring efficacy of antiresorptive therapies including postmenopausal osteoporosis treatment The assay is not intended as a screening test for osteoporosis. Measurements of bone turnover markers are not useful for the diagnosis of osteoporosis; diagnosis of osteoporosis should be made on the basis of bone density.

Interpretation: Bone alkaline phosphatase (BAP) concentration is high in Paget disease and osteomalacia. Antiresorptive therapies lower BAP from baseline measurements in Paget disease, osteomalacia, and osteoporosis. Several studies have shown that antiresorptive therapies for management of osteoporosis patients should result in at least a 25% decrease in BAP within 3 to 6 months of initiating therapy. BAP also decreases following antiresorptive therapy in Paget disease. When used as a marker for monitoring purposes, it is important to determine the critical difference (or least significant change). The critical difference is defined as the difference between 2 determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level.

Reference Values:
Males
- <2 years: 25-221 mcg/L
- 2-9 years: 27-148 mcg/L
- 10-13 years: 35-169 mcg/L
- 14-17 years: 13-111 mcg/L
- Adults: < or =20 mcg/L
Females
- <2 years: 28-187 mcg/L
- 2-9 years: 31-152 mcg/L
- 10-13 years: 19-177 mcg/L
- 14-17 years: 7-41 mcg/L
- Adults
  - Premenopausal: < or =14 mcg/L
  - Postmenopausal: < or =22 mcg/L

Bone Histomorphometry, Consultant Interpretation, Slides Only

Clinical Information: Bone histomorphometry is a very sophisticated procedure utilizing full thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases including renal osteodystrophy, osteomalacia, and osteoporosis. Other obtainable information relate to disorders such as aluminum toxicity and iron abnormalities.

Useful For: Identifying undetermined metabolic bone disease in submitted slide specimens Diagnosing renal osteodystrophy Diagnosing osteomalacia Diagnosing osteoporosis Diagnosing Paget disease Assessing the effects of therapy Identifying disorders of the hematopoietic system Diagnosing aluminum toxicity Identifying the presence of iron in the bone

Interpretation: Clinical endocrinologists trained in histomorphometric techniques review and interpret the histological appearance. A pathologist interprets the bone marrow from a hematoxylin and eosin-stained slide. No histomorphometric values are given.

Reference Values:
The laboratory will provide an interpretive report.


Bone Histomorphometry, Gross Microscopic Exam

Clinical Information: Bone histomorphometry is a very sophisticated procedure utilizing full-thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases, including renal osteodystrophy, osteomalacia, and osteoporosis, and other disorders such as aluminum toxicity and iron abnormalities.

Useful For: Undetermined metabolic bone disease in wet tissue specimens Renal osteodystrophy Osteomalacia Osteoporosis Paget disease Assessing effects of therapy Identification of some disorders of the hematopoietic system Aluminum toxicity Presence of iron in the bone

Interpretation: Computer-generated histomorphometric values are given for adequate specimens. Normal histomorphometric values for iliac crest are provided (female only). An interpretive report will be provided.

Reference Values:
The laboratory will provide a quantitative and an interpretive report.


Bone Marrow Aspirate (Bill Only)

Reference Values:
This test is for billing purposes only.

Bone Marrow Biopsy (Bill Only)

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

Bone Marrow Clot (Bill Only)

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

Bordetella pertussis and Bordetella parapertussis, Molecular Detection, PCR, Varies

Clinical Information: Bordetella pertussis is the highly contagious etiological agent of pertussis or whooping cough. Bordetella parapertussis causes a similar, but generally less severe illness. Despite vaccination efforts, B pertussis remains common in the United States, underscoring the need for effective diagnostic tests. In the United States, pertussis is most common in the late summer months. Pertussis vaccination does not prevent B parapertussis infection, which generally occurs in a younger age group than disease caused by B pertussis. Diagnosis of pertussis is based on having a high clinical index of suspicion for the infection, along with confirmation by laboratory testing. Laboratory testing methods include nucleic acid amplification tests (eg, PCR), serology, culture and direct fluorescent antibody testing. Culture and direct fluorescent antibody testing are limited by low sensitivity, rendering nucleic acid amplification tests and serology the tests of choice. The Centers for Disease Control and Prevention recommends PCR testing for patients suspected of having acute pertussis. B pertussis PCR detects roughly twice as many cases as culture. B pertussis DNA can be detected up to 4 weeks, or longer (up to 8 weeks in our experience), after symptom onset. However, over time, the amount of B pertussis and B parapertussis DNA will diminish, rendering the assay less sensitive. A serologic response to B pertussis is typically mounted by 2 weeks following infection and, therefore, detection of IgG-class antibodies to pertussis toxin (PT), which is only produced by B pertussis, can be a useful adjunct for diagnosis at later stages of illness at a time when the amount of B pertussis may be below the limit of detection of the PCR assay.

Useful For: Preferred diagnostic test for the detection of Bordetella pertussis or Bordetella parapertussis.

Interpretation: A positive result indicates the presence of DNA from Bordetella pertussis or B parapertussis. In some cases, a patient may test positive for both B pertussis and B parapertussis. Cross-reactivity with B holmesii and B bronchiseptica may occur with the B pertussis assay (see Cautions). A negative result indicates the absence of detectable B pertussis and B parapertussis DNA in the specimen but does not negate the presence of organism or active or recent disease (known inhibition rate of <1%) and may occur due to inhibition of PCR, sequence variability underlying primers and/or probes, or the presence of B pertussis or B parapertussis in quantities less than the limit of detection of the assay. Additionally, patients presenting late after symptom onset may test negative; in such cases, testing for B pertussis antibody, IgG, in serum may be considered.

Reference Values: Not applicable


Bordetella pertussis Antibody, IgG, Serum

Clinical Information: Bordetella pertussis, the causative agent of whooping cough, is highly contagious and remains endemic in the United States despite the high rate of vaccination. Acute B pertussis infections are typically diagnosed by culture or nucleic acid amplification testing (NAAT). However, symptomatic adults and adolescents often seek medical attention later in the course of infection, at which time the sensitivity of these 2 methods to detect the infectious agent decreases. A serologic response to B pertussis is typically mounted 2 weeks following infection, and therefore, detection of IgG-class antibodies to pertussis toxin (PT), which is only produced by B pertussis, can be a useful adjunct for diagnosis at later stages of illness. Prior to testing, providers should review whether the patient was recently vaccinated using the Tdap (Tetanus-Diphtheria-acellular Pertussis) or DTap vaccines. The acellular pertussis vaccine contains 1 to 5 B pertussis antigens, including filamentous hemagglutinin, pertactin, 2 fimbrial agglutinogens, and significant levels of PT. Therefore, recent vaccination for B pertussis, specifically within the last 2 to 6 months, may lead to a positive result by the anti-PT IgG assay, and knowledge of the patient’s vaccination history is important for accurate result interpretation.

Useful For: Diagnosis of recent infection with Bordetella pertussis in patients with symptoms consistent with whooping cough for 2 or more weeks. This test should not be used in neonates, young infants, or in children between the ages of 4 to 7 years as the routine childhood vaccine schedule may interfere with result interpretation. This test should not be used as a test of cure, to monitor response to treatment, or to determine vaccine status.

Interpretation: Negative (<40 IU/mL): No IgG antibodies to pertussis toxin (PT) detected. Results may be falsely negative in patients with less than 2 weeks of symptoms. Borderline (40-<100 IU/mL): Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive (> or =100 IU/mL): IgG antibodies to pertussis toxin (PT) detected. Results suggest recent infection with or recent vaccination against Bordetella pertussis.

Reference Values:
> or =100 IU/mL (positive)
> or = 40-<100 IU/mL (borderline)
<40 IU/mL (negative)

Reference values apply to all ages.


Boron, Serum/Plasma

Interpretation: Specimens for elemental testing should be collected in certified metal-free containers. Elevated results for elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen.

Reference Values:
Reporting limit determined each analysis

Normally: Less than 100 mcg/L
**Borrelia miyamotoi Detection PCR, Blood**

**Clinical Information:** Borrelia miyamotoi is a spirochetal bacterium that is closely related to the Borrelia species that cause tick-borne relapsing fever (TBRF), and it is more distantly related to the Borrelia species that cause Lyme disease. This organism causes a febrile illness like TBRF, with body and joint pain, fatigue, and rarely, rash, and has been detected in Ixodes scapularis and I pacificus ticks. These ticks are also the vectors for Lyme disease, anaplasmosis, and babesiosis. The preferred method for detecting B miyamotoi is real-time PCR. Less sensitive and specific methods for detecting B miyamotoi and agents of TBRF include identification of spirochetes in peripheral blood films, spinal fluid preparations, and serologic testing. This assay does not detect the Borrelia species that cause Lyme disease.

**Useful For:** Aids in the diagnosis of Borrelia miyamotoi infection in conjunction with clinical findings

**Interpretation:** A positive result indicates the presence of Borrelia miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever.

**Reference Values:**

Negative

**Clinical References:**

**Borrelia miyamotoi Detection PCR, Spinal Fluid**

**Clinical Information:** Borrelia miyamotoi is a spirochetal bacterium that is closely related to the Borrelia species that cause tick-borne relapsing fever (TBRF), and it is more distantly related to the Borrelia species that cause Lyme disease. This organism causes a febrile illness like TBRF, with body and joint pain, fatigue, and rarely, rash, and has been detected in Ixodes scapularis and I pacificus ticks. These ticks are also the vectors for Lyme disease, anaplasmosis, and babesiosis. The preferred method for detecting B miyamotoi is real-time PCR. Less sensitive and specific methods for detecting B miyamotoi and agents of TBRF include identification of spirochetes in peripheral blood films, cerebrospinal fluid (CSF) preparations, and serologic testing. This assay does not detect the Borrelia species that cause Lyme disease.

**Useful For:** Aids in the diagnosis of Borrelia miyamotoi infection in conjunction with clinical findings

**Interpretation:** A positive result indicates the presence of Borrelia miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever.

**Reference Values:**

Negative

**Clinical References:**
**Botrytis cinerea, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Botrytis cinerea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
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<td>3.50-17.4</td>
<td>Positive</td>
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<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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</tbody>
</table>


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**Bovine Serum Albumin, IgE, Serum**

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

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

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

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**Box Elder/Maple, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to box elder/maple Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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


BRACH 70366

Brachyury Immunostain, Technical Component Only

Clinical Information: Brachyury expression is required for the specification of mesodermal identity, representing one of the key genes regulating notochord formation. The brachyury gene, a T-box transcription factor, is uniquely expressed in chordomas.

Useful For: Aiding in the identification of chordomas

Interpretation: This test does not include pathologist interpretation only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


BBRAF 35893

BRAF Analysis (Bill Only)

Reference Values: This test is for billing purposes only.

This is not an orderable test.

BRAFV 70367

BRAF V600E Immunostain, Technical Component Only

Clinical Information: BRAF is a serine/threonine protein kinase and a member of the Raf family.
The BRAF V600E alteration leads to constitutive activation of the mitogen activated protein kinase pathway, which plays a role in cell proliferation and tumorigenesis. This genetic alteration has been detected in a variety of tumors such as melanoma, colorectal cancer, papillary thyroid carcinoma, hairy cell leukemia, Langerhans cell histiocytosis, and pleomorphic xanthoastrocytomas.

**Useful For:** Identification of BRAF V600E-mutated protein

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**BRAF V600E/V600K Somatic Mutation Analysis, Tumor**

**Clinical Information:** This test assesses for somatic (tumor-specific) BRAF V600E and V600K alterations. The BRAF gene is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression and BRAF alterations occur frequently in many different tumor types. BRAF variant analysis aids in the diagnosis of cancer types including anaplastic and papillary thyroid carcinoma, hairy cell leukemia, and papillary craniopharyngioma. BRAF V600E and V600K alterations are associated with response or resistance to specific targeted therapies in cancers such as melanoma, colorectal cancer, and lung cancer. Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. BRAF variant analysis can provide helpful diagnostic information in the context of evaluation for Lynch syndrome. See Lynch Syndrome Testing Algorithm in Special Instructions.

**Useful For:** Therapy selection for patients with cancer (eg, melanomas that may respond to BRAF inhibitors, colon cancers than may not respond to EGFR inhibitors) Aiding in the diagnosis/prognosis of certain cancers (eg, hairy cell leukemia, papillary thyroid cancers, and association with aggressiveness) Aid in determining risk for Lynch syndrome (eg, an adjunct to negative MLH1 germline testing in cases where colon tumor demonstrates MSI-H and loss of MLH1 protein expression)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
FBNC1
Brazil Nut Component rBer e 1

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Strongly positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.10 kU/L

BRAZ
Brazil Nut, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to Brazil nut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</tr>
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</table>

Reference values apply to all ages.
Breast Carcinoma-Associated Antigen, Serum

Clinical Information: Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens, which are large-molecular-weight glycoproteins with O-linked oligosaccharide chains. Monoclonal antibodies directed against these antigens have been developed, and several immunoassays are available to quantitate the levels of tumor-associated mucinous antigens in serum. The antibodies recognize epitopes of a breast cancer-associated antigen encoded by the human mucin 1 (MUC-1) gene, which is known by several names including MAM6, milk mucin antigen, cancer antigen (CA) 27.29, and CA 15-3. While CA 27.29 is expressed at the apical surface of normal epithelial cells, it is present throughout malignant epithelial cells of the breast, lung, ovary, pancreas, and other sites. The cancer-associated form of the antigen is less extensively glycosylated than the normal form and more specific for tumor cells.

Useful For: Serial testing in women with prior stage II or III breast cancer who are clinically free of disease Predicting early recurrence of disease in women with treated carcinoma of the breast Indicating that additional tests or procedures should be performed to confirm recurrence of breast cancer This test is not useful for screening women for carcinoma of the breast.

Interpretation: Increased levels of cancer-associated antigen (CA 27.29) (>38 U/mL) may indicate recurrent disease in a woman with treated breast carcinoma.

Reference Values:
Males
> or =18 years: < or =38.0 U/mL (use not defined)
Females
> or =18 years: < or =38.0 U/mL
Reference values have not been established for patients who are <18 years of age. Serum markers are not specific for malignancy, and values may vary by method.


BRG1 (SMARCA4) Immunostain, Technical Component Only

Clinical Information: BRG1 (SMARCA4) is a member of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex. Biallelic mutations in BRG1 (SMARCA4) have been reported in ovarian small cell carcinoma of hypercalcemic type (SCCOHT), amongst other tumors. Tumors with these mutations demonstrate a loss of BRG1 protein expression in the nucleus. SCCOHT is difficult to diagnose and loss of BRG1 expression can help in differentiating SCCOHT from its mimics including other primary or metastatic tumors of the ovaries.

Useful For: Diagnosing ovarian small cell carcinoma of hypercalcemic type (SCCOHT)

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is
available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**FBRIV**
**Brivaracetam, Plasma**

**Clinical Information:** The recommended steady-state brivaracetam plasma concentration for seizure control is 0.2 to 2.0 mcg/mL.

**Reference Values:**
Reporting limit determined each analysis
Units: mcg/mL

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**BRBPS**
**Broad Range Bacterial PCR and Sequencing, Varies**

**Clinical Information:** Cultures from patients with suspected bacterial infection involving normally sterile sites may fail to provide bacterial (including mycobacterial) growth for identification due to the presence of fastidious or slow-growing bacteria or as a result of antecedent antimicrobial chemotherapy. Polymerase chain reaction (PCR) amplification of a portion of the 16S ribosomal RNA gene followed by sequencing of the amplified product can be used to detect bacterial (including mycobacterial) nucleic acids in such situations, enabling a diagnosis. Sterile sources accepted for testing may have more than one bacterial species present or the presence of copy variants of the 16S rRNA gene within a single bacterial species, confounding Sanger sequencing analysis. Next-generation sequencing (NGS) can be useful in such cases. Ideal specimens are those in which bacteria (includes mycobacteria) are visualized by microscopy. Heart valves from patients with endocarditis with positive Gram stains are, for example, especially suitable.

**Useful For:** Detecting and identifying bacteria (including mycobacteria) from normally sterile sources, including synovial fluid; body fluids such as pleural, peritoneal, and pericardial fluids, cerebrospinal fluid (CSF); and both fresh and formalin-fixed paraffin-embedded (FFPE) tissues This test is not recommended as a test of cure because nucleic acids may persist for long periods of time after successful treatment.

**Interpretation:** A positive broad-range polymerase chain reaction (PCR)/sequencing result indicates that bacterial nucleic acid of the specified organism was detected, which may be due to bacterial infection or environmental or contaminating nucleic acids in the specimen. A negative broad-range PCR/sequencing result indicates the absence of detectable bacterial (including mycobacterial) nucleic acids in the specimen but does not rule-out false-negative results that may occur due to sampling error, sequence variability underlying the primers, the presence of bacterial nucleic acids in quantities less than the limit of detection of the assay, or inhibition of PCR. If PCR testing appears to be negative but there is evidence of PCR inhibition, testing will be repeated. If inhibition is again detected, the result will be reported as "PCR inhibition present."

**Reference Values:**
No bacterial DNA detected

**Clinical References:**
1. Oyvind K, Simmon K, Karaca D, Langeland N, Wiker HG: Dual priming oligonucleotides for broad-range amplification of the bacterial 16S rRNA gene directly from human
Broccoli IgG

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

## Broccoli, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to broccoli Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


BROM 82919

**Brome Grass, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to brome grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Bromine - Total, Blood

Reference Values:
Reporting limit determined each analysis.

Units: mg/L

The population reference interval derived from NMS Labs data (n=136) is usually between 1.4 and 8.8 mg/L (2.5th - 97.5th percentiles). Background concentrations are diet dependent. Workers exposed to methyl bromide with blood bromide concentrations greater than 12 mg/L have shown 3.5 times higher risk of electroencephalogram disturbances than compared to those with normal levels.

Brucella Antibody Screen, IgM and IgG, ELISA, Serum

Clinical Information: Brucellosis, major disease in humans and domesticated animals, is a systemic bacterial infection caused by Gram negative coccobacilli of the genus Brucella. Brucellosis is a zoonotic disease and a variety of domestic animals serve as reservoir species: Brucella infects goats (Brucella melitensis), cattle (Brucella abortus), swine (Brucella suis), and dogs (Brucella canis). Transmission to humans results from direct contact with infected animals, exposure to infectious aerosols, or ingestion of unpasteurized dairy products; human-to-human transmission does not occur. While few cases are reported in the US, the majority of cases occur in the Mediterranean region, Western Asia, and parts of Latin America and Africa. Three species of Brucella commonly cause disease in humans: B melitensis, B suis, and B abortus. Clinical manifestations of brucellosis consist of fever, sweats, malaise, weight loss, headache, and weakness. The onset may be insidious or acute, generally beginning within 2 to 4 weeks after exposure. Any organ or system of the body may be involved, although death is uncommon. Presumptive diagnosis of brucellosis can be made by detection of high or rising titers of specific antibodies, typically to smooth lipopolysaccharide (S-LPS), a major antigenic virulence determinant. Serologic tests using S-LPS can detect antibody to the three major Brucella species due to this shared epitope. IgM antibodies appear during the first week of infection followed by a switch to IgG synthesis during the second week. A variety of serologic tests have been used for diagnosis of Brucella infection. Detection of anti-Brucella antibodies using ELISA has been demonstrated to be a sensitive diagnostic approach. However, all specimens testing positive by an ELISA should be confirmed by an agglutination method as a means to increase assay specificity.

Useful For: Evaluating patients with suspected brucellosis

Interpretation: In the acute stage of the disease, there is an initial production of IgM antibodies followed closely by production of IgG antibodies. IgG-class antibodies may decline after treatment; however, high levels of circulating IgG-class antibodies may be found without any active disease. Rising levels of specific antibody in paired sera can be regarded as serological evidence of recent infection. The presence of specific IgM in a single specimen may also indicate a recent infection, although IgM-class antibodies may persist for months following acute disease. The CDC recommends that specimens testing positive for IgG or IgM by ELISA be confirmed by a Brucella-specific agglutination method.(1) The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes 1) isolation of Brucella species from a clinical specimen, 2) four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens obtained more than 2 weeks apart and studied at the same laboratory, and/or 3) demonstration by immunofluorescence of Brucella species in a clinical specimen. Positive results by ELISA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 14 to 21 days. If results of ELISA are negative and a recent infection is suspected, a new specimen should be tested after 14 to 21 days.

Reference Values:
IgG SCREEN
Negative

IgM SCREEN
Negative
Negative
Reference values apply to all ages.


BRUCB
87345

Brucella Culture, Blood

Clinical Information: Brucella species are facultative intracellular Gram-negative-staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, B suis, B melitensis, and occasionally B canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from blood, fluid (including urine), or tissue specimens.

Useful For: Diagnosis of brucellosis in blood specimens

Interpretation: Isolation of a Brucella species indicates infection. Cultures of blood and/or bone marrow are positive in 70% to 90% of acute Brucella infections, but much less so in subacute or chronic infections. In these latter instances, culture yield is highest from the specific tissue involved, or serology may be necessary to establish diagnosis.

Reference Values:
No growth after 14 days


BRUC
8077

Brucella Culture, Varies

Clinical Information: Brucella species are facultative intracellular Gram-negative staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, B suis, B melitensis, and occasionally B canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from blood, fluid (including urine), or tissue specimens.

Useful For: Diagnosis of brucellosis

Interpretation: Isolation of a Brucella species indicates infection. Cultures of blood and/or bone marrow are positive in 70% to 90% of acute Brucella infections, but much less so in subacute or chronic infections. In these latter instances, culture yield is highest from the specific tissue involved, or serology may be necessary to establish diagnosis.

Reference Values:
No growth after 14 days

Brucella Total Antibody Confirmation, Agglutination, Serum

**Clinical Information:** Brucella species are facultative intracellular, gram-negative staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, Brucella suis, Brucella melitensis, and occasionally Brucella canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from bone marrow, blood, fluid (including urine), or tissue specimens. In cases of suspected brucellosis, serology may assist in the diagnosis and play a supplementary role to routine culture. Antibodies to Brucella species may not become detectable until 1 to 2 weeks following the onset of symptoms, so serum specimens drawn during acute disease may be negative by serology in patients with brucellosis. If serology is performed, the Centers for Disease Control and Prevention currently recommends that specimens testing positive or equivocal for IgG or IgM by a screening enzyme immunoassay (EIA) be confirmed by a Brucella-specific agglutination method.(1)

**Useful For:** Evaluating patients with suspected brucellosis

**Interpretation:** The Centers for Disease Control and Prevention (CDC) recommends that specimens testing positive or equivocal for IgG or IgM by a screening enzyme immunoassay (EIA) be confirmed by a Brucella-specific agglutination method.(1) Negative to a titer of 1:40 or higher can be seen in the normal, healthy population. A titer of 1:80 or greater is often considered clinically significant(2); however, a 4-fold or greater increase in titer between acute and convalescent phase sera is required to diagnose acute infection. The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes 1) isolation of Brucella species from a clinical specimen, 2) four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens drawn more than 2 weeks apart and studied at the same laboratory, or 3) demonstration by immunofluorescence of Brucella species in a clinical specimen. Positive results by a screening EIA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 7 to 14 days.

**Reference Values:**
<1:80

SUNDS) due to the tendency for syncope and sudden cardiac death to occur at rest or during sleep. The most common presentation of BrS is a male in his 40s with a history of syncopal episodes and malignant arrhythmias. However, presentation may occur at any age including infancy, where BrS may present as SIDS (sudden infant death syndrome). Published studies indicate that BrS is responsible for 4% to 12% of unexpected sudden deaths and for up to 20% of all sudden death in individuals with a structurally normal heart. The prevalence of BrS in the general population is difficult to determine due to the challenges of diagnosing the condition. In Southeast Asia where SUNDS is endemic, the prevalence of BrS is estimated to be 1 in 2,000. Of note, men are 8 to 10 times more likely to express symptoms of BrS, but the disease affects females as well and both sexes are at risk for ventricular arrhythmia and sudden death. Approximately 25% to 30% of BrS is accounted for by pathogenic variants in the genes known to cause the disorder, with the majority of cases attributed to the SCN5A gene. Although the majority of pathogenic variants identified to date have been detected by sequence analysis, large deletions in the SCN5A, SCN3B, CACNA1C, and KCNE3 genes have been reported in BrS. Genetic testing for BrS is supported by multiple consensus statements to confirm the diagnosis and identify at-risk family members. This is particularly important because the majority of patients with BrS are asymptomatic, but asymptomatic individuals may still be at increased risk for cardiac events. Pre- and posttest genetic counseling is an important factor in the diagnosis and management of BrS and is supported by expert consensus statements.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Brugada syndrome (BrS) Establishing a diagnosis of a BrS, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


Brussels Sprouts, IgE, Serum

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

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

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

**Reference Values:**

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<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<td>Negative</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**BTKFP 89742**

**Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry, Blood**

**Clinical Information:** X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK,(1) which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood.(2) Approximately 85% of male patients with defects in early B-cell development have XLA.(3) Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key clinical diagnostic characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year of age. BTK, the only gene associated with XLA, maps to the X-chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA.(4) BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Bruton tyrosine kinase (Btk) protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Variants causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Missense variants account for 40% of all variants, while nonsense variants account for 17%, deletions 20%, insertions 7%, and splice-site variants 16%. Over 600 unique variants in the BTK gene have been detected by full gene sequencing and are listed in BTKbase, a database for BTK variants (http://bioinf.uta.fi/BTKbase).(5)
Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense variants are overrepresented 4-fold compared to substitutions, which indicates that the latter may be tolerated without causing a phenotype. The type and location of the variant in the gene clearly affects the severity of the clinical phenotype. Some variants manifest within the first year or 2 of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood. (5) Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same variant is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK variant. (5) Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate (6) and for XLA, if a male parent is affected with the disease. A flow cytometry test for intracellular Btk in monocytes using an anti-Btk monoclonal antibody was developed by Futatani et al, which was used to evaluate both XLA patients and carriers. (7) In this study, 41 unrelated XLA families were studied and deficient Btk protein expression was seen in 40 of these 41 patients, with complete Btk deficiency in 35 patients and partial Btk deficiency in 5 patients. One patient had a normal level of Btk protein expression. The 6 patients with partial or normal Btk expression had missense BTK variants. Additionally, the flow cytometry assay detected carrier status in the mothers of 35 of the 41 patients (approximately 85%). In the 6 patients where the Btk expression was normal in the mothers of XLA patients, it was noted that all these patients were sporadic cases without previous family history of the disease. (7) It appears, therefore, that most BTK variants result in deficient expression of Btk protein, which can be detected by flow cytometry in monocytes. (7,8) Also, the mosaic expression of Btk protein in the monocytes by flow cytometry is potentially useful in the diagnosis of female carriers. (8) The flow cytometry test therefore provides a convenient screening tool for the diagnosis of XLA with confirmation of the diagnosis by BTK genotyping. (7,8) In the rare patient with the clinical features of XLA but normal Btk protein expression, BTK genotyping must be performed to determine the presence of a variant. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). As well, some BTK variants can preserve small numbers of circulating B cells and, therefore, all 3 criteria mentioned above need to be evaluated. Patients should be assessed for the presence of Btk protein by flow cytometry, although normal results by flow cytometry do not rule out the presence of a BTK variant with aberrant protein function (despite normal protein expression). The diagnosis is established or confirmed only in those individuals who have a variant identified in the BTK gene by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells. Appropriate clinical history is required with or without abnormal Btk protein results by flow cytometry. It was shown that there are XLA patients with mothers who have normal Btk protein expression by flow cytometry and normal BTK genotyping and that the variant in the patient is a result of de novo variants in the maternal germline. In the same study, it was shown that there can be female carriers who have normal Btk protein expression but are genetically heterozygous and they do not show abnormal protein expression due to extreme skewed inactivation of the mutant X-chromosome. (6) Also, the presence of 1 copy of the normal BTK gene and associated normal Btk protein can stabilize mutant protein abrogating the typical bimodal pattern of protein expression seen in female carriers. Therefore, female carrier status can only conclusively be determined by genetic testing, especially if the Btk protein flow test is normal. It is important to keep in mind that the mere presence of BTK gene variants does not necessarily correlate with a diagnosis of XLA unless the appropriate clinical and immunological features are present. (9,10)

**Useful For:** Preferred test for confirming a diagnosis of X-linked agammaglobulinemia (XLA) in males with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and below 1% peripheral B cells In females, this is the most useful test for identifying carriers of XLA. By including protein and gene analysis, this test provides a comprehensive assessment and enables appropriate genotype-phenotype correlations.

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**

BTKSP: An interpretive report will be provided.
BTK: Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).


Bruton Tyrosine Kinase (BTK) Genotype, Full Gene Sequence, Blood

Clinical Information: X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK),(1) which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood.(2) Approximately 85% of male patients with defects in early B-cell development have XLA.(3) Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key diagnostic clinical characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year. BTK, the only gene associated with XLA, maps to the X chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA.(4) BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Btk protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Variants causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Over 800 unique variants in BTK have been detected by full gene sequencing and are listed in BTKbase, a database for BTK variants (http://structure.bmc.lu.se/idbase/BTKbase/).(5) Missense variants account for approximately 33% of unique variants, nonsense variants 13%, frameshift 25%, in-frame deletions and insertions 4%, large deletions 3% to 5%, and intronic and complex variants make up the remainder. Patients with a large deletion spanning the BTK gene may also impact the adjacent TIMM8A gene (also known as DDP) resulting in both XLA and deafness-dystonia-optic neuropathy syndrome (DDS or Mohr-Tranebjærg syndrome). Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense and frameshift variants are overrepresented 4-fold compared with substitutions, which indicates that the latter may be tolerated without causing a phenotype or with a milder phenotype or later age at presentation. Some individuals present within the first 2 years of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood.(5) Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same variant is present. While the disease is considered fully penetrant, the
clinical phenotype can vary considerably depending on the nature of the specific BTK variant. Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate and for XLA, if a male parent is affected with the disease. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). Conversely, some BTK variants can preserve small numbers of circulating B cells and, therefore, all 3 of the criteria mentioned above need to be evaluated. The preferred approach for confirming a diagnosis of XLA in males and identifying carrier females requires testing for the Btk protein expression on B cells by flow cytometry and genetic testing for a BTK variant. Patients can be screened for the presence of Btk protein by flow cytometry (BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood); however, normal results by flow cytometry do not rule out the presence of a BTK variant with normal protein expression but aberrant protein function. The diagnosis is confirmed only in those individuals with appropriate clinical history who have a variant identified within BTK by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells.

**Useful For:** Confirming a diagnosis of X-linked agammaglobulinemia (XLA) in male patients with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and less than 1% peripheral B cells, with or without abnormal Bruton tyrosine kinase (Btk) protein expression by flow cytometry Evaluating for the presence of BTK variants in female relatives (of male XLA patients) who do not demonstrate carrier phenotype by Btk flow cytometry

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BTK (Bruton Tyrosine Kinase) protein expression by flow cytometry**

**Clinical Information:** The differential diagnosis for patients with primary hypogammaglobulinemia of unclear etiology (after other secondary causes of hypogammaglobulinemia have been ruled out) includes common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA). CVID is the most common diagnosis of humoral immunodeficiency, particularly in adults, but also in children over 4 years of age. However, adult male patients with XLA may be misdiagnosed with CVID. XLA is an independent humoral immunodeficiency and should not be regarded as a subset of CVID. The BTK gene is present on the long arm of the X-chromosome and encodes for a cytoplasmic tyrosine kinase with 5 distinct structural domains. While BTK gene sequencing is the gold standard for definitively identifying mutations and confirming a diagnosis of XLA, it is labor intensive and expensive. Flow cytometry is a screening test for XLA and should be included in the evaluation of patients with possible CVID, particularly in male patients with less than 1% B cells. Bruton tyrosine kinase (Btk) is an intracellular
protein and absence of the Btk protein by flow cytometry provides a strong rationale for performing a BTK gene-sequencing test. However, 20% to 30% of XLA patients may have intact or truncated Btk protein with abnormal function; therefore, genetic analysis remains the more definitive test for diagnosing XLA (besides other clinical and immunological parameters). XLA is a prototypical humoral immunodeficiency caused by mutations in the BTK gene, which encodes Btk, a hematopoietic-specific tyrosine kinase. XLA is characterized by normal, reduced, or absent Btk expression in monocytes and platelets, a significant reduction or absence of circulating B cells in blood, and profound hypogammaglobulinemia of all isotypes (IgG, IgA, IgM, and IgE). The clinical presentation includes early onset of recurrent bacterial infections, and absent lymph nodes and tonsils. Btk plays a critical role in B-cell differentiation. The defect in Btk may be "leaky" in some patients (ie, a consequence of mutations in the gene that result in a milder clinical and laboratory phenotype), such that these patients may have some levels of IgG and/or IgM and a small number of B cells in blood.(1) The vast majority of XLA patients are diagnosed in childhood (median age of diagnosis in patients with sporadic XLA is 26 months), although some patients are recognized in early adulthood or later in life. The diagnosis of XLA in both children and adults indicates that the disorder demonstrates considerable clinical phenotypic heterogeneity, depending on the position of the mutations within the gene. Females are typically carriers and asymptomatic. Testing in adult females should be limited to those in their child-bearing years (<45 years). Carrier testing ideally should be confirmed by genetic testing since it is possible to have a normal flow cytometry test for protein expression in the presence of heterozygous (carrier) BTK gene mutations. Flow cytometry is a preliminary screening test for XLA. It is important to keep in mind that this flow cytometry test is only a screening tool and approximately 20% to 30% of patients who have a mutation within the BTK gene have normal protein expression (again related to the position of the mutation in the gene and the antibody used for flow cytometric analysis). Therefore, in addition to clinical correlation, genetic testing is recommended to confirm a diagnosis of XLA. Furthermore, it is helpful to correlate gene and protein data with clinical history (genotype-phenotype correlation) in making a final diagnosis of XLA. Consequently, the preferred test for XLA is BTKFP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry, which includes both flow cytometry and gene sequencing to confirm the presence of a BTK mutation. If a familial mutation has already been identified, then BTKMP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry should be ordered.

**Useful For:** Preliminary screening for X-linked agammaglobulinemia (XLA), primarily in male patients (<65 years of age) or female carriers (child-bearing age: <45 years) Because genotype-phenotype correlations are important, the preferred test for confirming a diagnosis of XLA in males and identifying carrier females is: -BTKFP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry -In families where a BTK mutation has already been identified, order BTKMP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry

**Interpretation:** Results are reported as Bruton tyrosine kinase (Btk) protein expression present (normal) or absent (abnormal) in monocytes. Additionally, mosaic Btk expression (indicative of a carrier) and reduced Btk expression (consistent with partial Btk protein deficiency) are reported when present and correlated with a healthy experimental control. BTK genotyping (BTKS / Bruton Tyrosine Kinase (BTK) Genotype, Full Gene Sequence or BTKK / Bruton Tyrosine Kinase (BTK) Genotype, Known Mutation) should be performed in the following situations: -To confirm any abnormal flow cytometry result -In the rare patient with the clinical features of X-linked agammaglobulinemia (XLA), but normal Btk protein expression -In mothers of patients who do not show the classic carrier pattern of bimodal protein expression (to determine if there is maternal germinal mosaicism or skewed mutant X-chromosome inactivation) or there is dominant expression of the normal protein in the presence of 1 copy of a mutation.

**Reference Values:**
Present

Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).

Buckwheat, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to buckwheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>0.70-3.49</td>
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<td>3.50-17.4</td>
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<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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</tbody>
</table>

Reference values apply to all ages.

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

**Useful For:** Establishing a diagnosis of an allergy to Budgerigar droppings Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
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Reference values apply to all ages.

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

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</tbody>
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Reference values apply to all ages.


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**Bullous Pemphigoid, BP180 and BP230, IgG Antibodies, Serum**

**Clinical Information:** Bullous pemphigoid (BP) is a chronic pruritic blistering disorder found mainly in aged persons, characterized by the development of tense blisters over an erythematous or urticarial base. IgG-antibasement membrane zone antibodies are found in the serum of patients, and linear IgG and C3 sediment is found on the basement membrane zone of the lesion. Several well characterized variants exist including localized, mucous membrane predominant and pemphigoid gestationis, also referred to as herpes gestationis. Target antigens of the autoantibodies in BP patient serum are BP230 and BP180, also called BPAG1 and BPAG2. Molecular weight of these antigens is 230 kD and 180 kD, respectively. BP180 is thought to be the direct target of the autoantibody because of its location along the basement membranes, and the autoantibody against BP230 is thought to be secondarily produced.

**Useful For:** Initial screening test in the diagnosis of bullous pemphigoid and its variants

Complementing the standard serum test of indirect immunofluorescence utilizing monkey esophagus substrate and human salt-split skin substrate (CIFS / Cutaneous Immunofluorescence Antibodies (IgG), Serum)

**Interpretation:** Antibodies to bullous pemphigoid (BP) BP180 and BP230 have been shown to be present in most patients with pemphigoid. Adequate sensitivities and specificity for disease are documented and Mayo Clinic's experience demonstrates a very good correlation between BP180 and BP230 results and the presence of pemphigoid (see Supportive Data). However, in those patients strongly suspected to have pemphigoid, either by clinical findings or by routine biopsy and/or direct immunofluorescence, and in whom the BP180/BP230 assay is negative, follow-up testing by CIFS / Cutaneous Immunofluorescence Antibodies (IgG), Serum is recommended. Antibody titer may correlates with disease activity in some patients. Patients with severe disease may be expected to have high titers of antibodies to BP. Titers may decrease with clinical improvement.

**Reference Values:**

BULLOUS PEMPHIGOID 180

<20 RU/mL (negative)

> or =20 RU/mL (positive)
BULLOUS PEMPHIGOID 230

<20 RU/mL (negative)
> or =20 RU/mL (positive)

Clinical References:

FMARC
75307
Bupivacaine (Marcaine)

Reference Values:
Reference Range: 0.1 - 4.0 ug/mL

BUPMX
65215
Buprenorphine and Norbuprenorphine, Chain of Custody, Random, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.(1) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids.(1) Compared to morphine, buprenorphine is 25 to 40 times more potent.(1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist.

Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one-fifth of the potency of its parent. The glucuronide metabolites are inactive.(1) The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have strayed from opioid dependence therapy. Chain of custody is a record of the disposition of a specimen to document the individuals that collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Monitoring of compliance of buprenorphine therapy Detection and confirmation of the illicit use of buprenorphine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.
**Reference Values:**

Negative

Cutoff concentrations:
- Buprenorphine: 5.0 ng/mL
- Norbuprenorphine: 2.5 ng/mL

**Clinical References:**

**BUPM 66200**

**Buprenorphine and Norbuprenorphine, Random, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin. Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent. As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one-fifth of the potency of its parent. The glucuronide metabolites are inactive. The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have strayed from opioid dependence therapy.

**Useful For:** Monitoring of compliance utilizing buprenorphine Detection and confirmation of the illicit use of buprenorphine

**Interpretation:** The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.

**Reference Values:**

Negative

Cutoff concentrations:
- Buprenorphine: 5.0 ng/mL
- Norbuprenorphine: 2.5 ng/mL

**Clinical References:**

**Buprenorphine Screen with Reflex, Random, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin. Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent. As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive.

This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can have a false-negative due to the antibody's ability to cross-react with different drugs in the target class.

**Useful For:** Screening for drug abuse or use of buprenorphine

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**

- **Negative**
- Screening cutoff concentration:
  - Buprenorphine: 5 ng/mL


**Buprenorphine Screen, Random, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin. Buprenorphine has a prolonged duration of activity. The combination of decreased clinical
effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent. (1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive. (1) This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can have a false-negative due to the antibody’s ability to cross-react with different drugs in the target class.

**Useful For:** Screening for drug abuse or use of buprenorphine

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
- Negative
- Screening cutoff concentration: Buprenorphine: 5 ng/mL


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**Bupropion and Metabolite, Serum**

**Interpretation:** Bupropion: Maximum antidepressant response was observed at trough plasma concentrations of 50 ng/mL bupropion with virtually no response below 25 ng/mL. Reported average bupropion peak plasma concentrations: Adults: Single 100 mg IR 120 +/- 10 ng/mL (Males): 150 +/- 10 ng/mL (Females) Adults: Single 200 mg IR 220 +/- 20 ng/mL (Males): 270 +/- 20 ng/mL (Females) Adults: Single 150 mg SR 140 +/- 20 ng/mL Juveniles: 100 mg/day SR for 2 weeks 25 +/- 8 ng/mL Juveniles: 200 mg/day SR for 2 weeks 53 +/- 22 ng/mL Specimens must be kept frozen. If specimens are not kept frozen, this may cause lower or negative values. Hydroxybupropion: 8 adults (Age 22 to 42) taking thrice daily 100 mg normal release bupropion for 2 weeks had an average peak plasma concentration of 1000 +/- 70 ng/mL hydroxybupropion. Juvenile patients taking once daily, extended release bupropion for two weeks had the following peak plasma concentrations: 100 mg/day (n = 11), 450 +/- 210 ng/mL hydroxybupropion 200 mg/day (n = 8), 710 +/- 350 ng/mL hydroxybupropion

**Reference Values:**
- Reporting Limit determined each analysis.
- Units: ng/mL

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**Buspirone (Buspar)**

**Reference Values:**
- Units: ng/mL

Therapeutic and toxic ranges have not been established.

Expected serum buspirone concentrations in patients taking recommended daily dosages: up to 10.00 ng/mL.
Busulfan, Intravenous Dose, Area Under the Curve, Plasma

Clinical Information: Busulfan is an alkylating agent used to ablate bone marrow cells prior to hematopoietic stem cell transplantation for chronic myelogenous leukemia. Busulfan is typically administered intravenously (IV) at the recommended dosage of 0.8 mg/kg of actual or ideal body weight (whichever is lower) and given once every 6 hours over 4 days for a total of 16 doses. Dose-limiting toxicity of busulfan includes veno-occlusive liver disease, seizures, and coma. To avoid toxicity while ensuring busulfan dose adequacy to completely ablate the bone marrow, IV dosing should be guided by a pharmacokinetic (PK) evaluation of the area under the curve (AUC) and clearance after the first dose. The PK evaluation should be carried out at the end of the first dose, with results of PK testing available to facilitate dose adjustment before beginning the fifth dose.

Useful For: Guiding dosage adjustments to achieve complete bone marrow ablation while minimizing dose-dependent toxicity

Interpretation: Results of the timed collections will be used to calculate a 6-hour area under the curve (AUC). If a different dosing or specimen collection protocol is used, or if different calculations are required, contact the Laboratory Director. The optimal result for AUC (6 hour) derived from this pharmacokinetic (PK) evaluation of IV busulfan is 1100 (mcmol/L)(min). AUC results greater than 1500 (mcmol/L)(min) are associated with hepatic veno-occlusive disease. A dose reduction should be considered before the next busulfan infusion. AUC results below 900 (mcmol/L)(min) are consistent with incomplete bone marrow ablation. A dose increase should be considered before the next busulfan infusion. Clearance of busulfan in patients with normal renal function is usually in the range of 2.1 to 3.5 (mL/min)/kg. Elevated AUC is typically associated with clearance below 2.5 (mL/min)/kg, most frequently due to diminished activity of glutathione S-transferase A1-1 activity.

Reference Values:
AREA UNDER THE CURVE
900-1500 (mcmol/L)(min)

CLEARANCE
2.1-3.5 (mL/minute)/kg


Butalbital, Serum

Clinical Information: Butalbital, short-acting barbiturate with hypnotic properties, is used in combination with other drugs such as acetaminophen, salicylate, caffeine, and codeine. Butalbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a volume of distribution of 0.8 L/kg, and about 26% of a dose is bound to plasma proteins. The half-life of butalbital is about 35 to 88 hours. Excretion occurs mainly in the urine.
Useful For: Monitoring butalbital therapy

Interpretation: Butalbital concentrations of 10 mcg/mL or greater have been associated with toxicity.

Reference Values:
<10 mcg/mL


C-Peptide, Serum

Clinical Information: C-peptide (connecting peptide), a 31-amino-acid polypeptide, represents the midportion of the proinsulin molecule. Proinsulin resembles a hairpin structure, with an N-terminal and C-terminal, which correspond to the A and B chains of the mature insulin molecule, oriented parallel to each other and linked by disulfide bonds. The looped portion of the hairpin between the A and B chains is called C-peptide. During insulin secretion, C-peptide is enzymatically cleaved off and cosecreted in equimolar proportion with mature insulin molecules. Following secretion, insulin and C-peptide enter the portal circulation and are routed through the liver where at least 50% of the insulin binds to receptors, initiates specific hepatic actions (stimulation of hepatic glucose uptake and suppression of glycogenolysis, gluconeogenesis, and ketogenesis), and is subsequently degraded. Most of the insulin molecules that pass through the liver into the main circulation bind to peripheral insulin receptors, promoting glucose uptake, while the remaining molecules undergo renal elimination. Unlike insulin, C-peptide is subject to neither hepatic nor significant peripheral degradation but is mainly removed by the kidneys. As a result, C-peptide has a longer half-life than insulin (30-35 minutes versus 5-10 minutes), and the molar ratio of circulating insulin to circulating C-peptide is generally below 1, despite equimolar secretion. Until recently, C-peptide was thought to have no physiological function, but it now appears that there may be specific C-peptide cell-surface receptors (most likely belonging to the super-family of G-protein coupled receptors), which influence endothelial responsiveness and skeletal and renal blood flow. In most disease conditions associated with abnormal serum insulin levels, the changes in serum C-peptide levels parallel insulin-related alterations (insulin to C-peptide molar ratio < or =1). Both serum C-peptide and serum insulin levels are elevated in renal failure and in disease states that lead to augmented primary endogenous insulin secretion (eg, insulinoma, sulfonylurea intoxication). Both also may be raised in any disease states that cause secondary increases in endogenous insulin secretion mediated through insulin resistance, primarily obesity, glucose intolerance, and early type 2 diabetes mellitus (DM), as well as endocrine disorders associated with hypersecretion of insulin-antagonistic hormones (eg, Cushing syndrome, acromegaly). Failing insulin secretion in type 1 DM and longstanding type 2 DM is associated with corresponding reductions in serum C-peptide levels. Discordant serum insulin and serum C-peptide abnormalities are mainly observed in 2 situations: exogenous insulin administration and the presence of anti-insulin autoantibodies. Factitious hypoglycemia due to surreptitious insulin administration results in appropriate suppression of endogenous insulin and C-peptide secretion. At the same time, the peripherally administered insulin bypasses the hepatic first-pass metabolism. In these situations, insulin levels are elevated and C-peptide levels are decreased. In patients with insulin antibodies, insulin levels are increased because of the prolonged half-life of autoantibody-bound insulin. Some patients with anti-idiotypic anti-insulin autoantibodies experience episodic hypoglycemia caused by displacement of autoantibody-bound insulin.

Useful For: Diagnostic workup of hypoglycemia: -Diagnosis of factitious hypoglycemia due to surreptitious administration of insulin -Evaluation of possible insulinoma -Surrogate measure for the absence or presence of physiological suppressibility of endogenous insulin secretion during diagnostic insulin-induced hypoglycemia (C-peptide suppression test) Assessing insulin secretory reserve in selected diabetic patients (as listed below) who either have insulin autoantibodies or who are receiving insulin.
therapy: Assessing residual endogenous insulin secretory reserve - Monitoring pancreatic and islet cell transplant function - Monitoring immunomodulatory therapy aimed at slowing progression of preclinical, or very early stage type 1 diabetes mellitus

**Interpretation:** To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio):

- Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L
- Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L

Factitious hypoglycemia due to surreptitious insulin administration results in elevated serum insulin levels and low or undetectable C-peptide levels, with a clear reversal of the physiological molar insulin to C-peptide ratio (< or =1) to an insulin to C-peptide ratio of greater than 1.

By contrast, insulin and C-peptide levels are both elevated in insulinoma and the insulin to C-peptide molar ratio is 1 or less. Sulfonylurea ingestion also is associated with preservation of the insulin to C-peptide molar ratio of 1 or less. In patients with insulin autoantibodies, the insulin to C-peptide ratio may be reversed to greater than 1, because of the prolonged half-life of autoantibody-bound insulin.

Dynamic testing may be necessary in the workup of hypoglycemia; the C-peptide suppression test is most commonly employed. C-peptide levels are measured following induction of hypoglycemia through exogenous insulin administration. The test relies on the demonstration of the lack of suppression of serum C-peptide levels within 2 hours following insulin-induced hypoglycemia in patients with insulinoma. Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

**Reference Values:**

1.1–4.4 ng/mL

Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

**Clinical References:**


**C-Reactive Protein (CRP) Immunostain, Technical Component Only**

**Clinical Information:** C-reactive protein (CRP) is an acute-phase reactant associated with host defense that promotes agglutination and complement fixation. CRP can be used with a panel of immunohistochemical markers (beta-catenin, liver fatty acid-binding protein, glutamine synthetase, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. CRP, along with amyloid A, is overexpressed in inflammatory (type 3) hepatic adenoma. CRP may stain hepatocytes in nonneoplastic liver tissue in areas of nonspecific inflammation.

**Useful For:** Classification of hepatic adenomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
C-Reactive Protein (CRP), Serum

Clinical Information: C-reactive protein (CRP) is one of the most sensitive acute-phase reactants for inflammation. CRP is synthesized by the liver and consists of 5 identical polypeptide chains that form a 5-membered ring with a molecular weight of 105,000 daltons. Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever. CRP elevations are nonspecific and may be useful for the detection of systemic inflammatory processes; to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, eg, in patients suffering from systemic lupus erythematosus or colitis ulcerosa; to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy; to determine the presence of postoperative complications at an early stage, such as infected wounds, thrombosis, and pneumonia; and to distinguish between infection and bone marrow rejection. Postoperative monitoring of CRP levels of patients can aid in the recognition of unexpected complications (persisting high or increasing levels). Measuring changes in the concentration of CRP provides useful diagnostic information about the level of acuity and severity of a disease. It also allows judgments about the disease genesis. Persistence of a high serum CRP concentration is usually a grave prognostic sign that generally indicates the presence of an uncontrolled infection.

Useful For: Detecting systemic inflammatory processes Detecting infection and assessing response to antibiotic treatment of bacterial infections Differentiating between active and inactive disease forms with concurrent infection

Interpretation: In normal healthy individuals, C-reactive protein (CRP) is a trace protein (<8 mg/L). Elevated values are consistent with an acute inflammatory process. After onset of an acute phase response, the serum CRP concentration rises rapidly (within 6-12 hours and peaks at 24-48 hours) and extensively. Concentrations above 100 mg/L are associated with severe stimuli such as major trauma and severe infection (sepsis).

Reference Values: < or =8.0 mg/L


C-Reactive Protein, High Sensitivity, Serum

Clinical Information: C-reactive protein (CRP) is a biomarker of inflammation. Plasma CRP concentrations increase rapidly and dramatically (100-fold or more) in response to tissue injury or inflammation. High-sensitivity CRP (hs-CRP) is more precise than standard CRP when measuring baseline (ie, normal) concentrations and enables a measure of chronic inflammation. Atherosclerosis is an inflammatory disease and hs-CRP has been endorsed by multiple guidelines as a biomarker of atherosclerotic cardiovascular disease risk.(1-3) A large prospective clinical trial demonstrated significantly less cardiovascular risk for patients with hs-CRP less than 2.0 mg/L.(1) More aggressive treatment strategies may be warranted in patients with hs-CRP of 2.0 mg/L or higher.

Useful For: Assessment of risk of developing myocardial infarction in patients presenting with acute coronary syndromes Assessment of risk of developing cardiovascular disease or ischemic events in individuals who do not manifest disease at present

**Interpretation:** Values greater than 2.0 mg/L suggest an increased likelihood of developing cardiovascular disease or ischemic events.

**Reference Values:**
- Lower risk: <2.0 mg/L
- Higher risk: ≥2.0 mg/L
- Acute inflammation: >10.0 mg/L

**Clinical References:**
1. Package Insert: Cardiac C-Reactive Protein (Latex) High Sensitive, Roche Diagnostics. 03/2019

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**C1 Esterase Inhibitor Antigen, Serum**

**Clinical Information:** C1 esterase inhibitor blocks the activation of C1 (first component of the complement cascade) to its active form. The deficiency of C1 esterase inhibitor results in the inappropriate activation of C1 and the subsequent release of an activation peptide from C2 with kinin-like activity. This kinin-like peptide enhances vascular permeability. C1 esterase inhibitor deficiency results in hereditary or acquired angioedema. This disease is an autosomal dominant inherited condition, in which exhaustion of the abnormally low levels of C1 esterase inhibitor results in C1 activation, breakdown of C2 and C4, and subsequent acute edema of subcutaneous tissue, the gastrointestinal tract, or the upper respiratory tract. The disease responds to attenuated androgens. Because 15% of C1 inhibitor deficiencies have nonfunctional protein, some patients will have abnormal functional results (FC1EQ / C1 Esterase Inhibitor, Functional Assay, Serum) in the presence of normal (or elevated) antigen levels.

**Useful For:** Diagnosis of hereditary angioedema Monitoring levels of C1 esterase inhibitor in response to therapy

**Interpretation:** Abnormally low results are consistent with a heterozygous C1 esterase inhibitor deficiency and hereditary angioedema. Fifteen percent of hereditary angioedema patients have a normal or elevated level but nonfunctional C1 esterase inhibitor protein. Detection of these patients requires a functional measurement of C1 esterase inhibitor; FC1EQ / C1 Esterase Inhibitor, Functional Assay, Serum. Measurement of C1q antigen levels; C1Q / Complement C1q, Serum, is key to the differential diagnoses of acquired or hereditary angioedema. Those patients with the hereditary form of the disease will have normal levels of C1q, while those with the acquired form of the disease will have low levels. Studies in children show that adult levels of C1 inhibitor are reached by 6 months of age.

**Reference Values:**
- 19-37 mg/dL

**Clinical References:**
2. Gelfand JA, Boss GR, Conley CL, et al: Acquired C1 esterase inhibitor...

C1 Esterase Inhibitor, Functional Assay, Serum

Clinical Information: C1 inhibitor (C1-INH) is a multispecific protease inhibitor that is present in normal human plasma and serum, and which regulates enzymes of the complement, coagulation, fibrinolytic, and kinin-forming systems. The enzymes (proteases) regulated by this protein include the C1r and C1s subunits of the activated first component of complement, activated Hageman factor (factor XIIa), kallikrein (Fletcher factor), and plasmin. A deficiency of functionally active C1-INH may lead to life-threatening angioedema. Two major forms of C1-INH deficiency have been reported: the congenital form, termed hereditary angioedema (HAE), and the acquired form that is associated with a variety of diseases, including lymphoid malignancies. HAE is characterized by transient but recurrent attacks of nonpruritic swelling of various tissues throughout the body. The symptomatology depends upon the organs involved. Intestinal attacks lead to a diversity of symptoms including pain, cramps, vomiting, and diarrhea. The most frequent cause of death in this disease is airway obstruction secondary to laryngeal edema occurring during an attack. There are 2 types of HAE that can be distinguished biochemically. Patients with the more common type (85% of HAE patients) have low levels of functional C1-INH and C1-INH antigen. Patients with the second form (15% of HAE patients) have low levels of functional C1-INH but normal or increased levels of C1-INH antigen that is dysfunctional. The variable nature of the symptoms at different time periods during the course of the disease makes it difficult to make a definitive diagnosis based solely on clinical observation.

Useful For: Diagnosing hereditary angioedema and for monitoring response to therapy

Interpretation: Hereditary angioedema (HAE) can be definitely diagnosed by laboratory tests demonstrating a marked reduction in C1 inhibitor (C1-INH) antigen or abnormally low functional C1-INH levels in a patient's plasma or serum that has normal or elevated antigen. Nonfunctional results are consistent with HAE. Patients with current attacks will also have low C2 and C4 levels due to C1 activation and complement consumption. Patients with acquired C1-INH deficiency have a low C1q in addition to low C1-INH.

Reference Values:
>67% normal (normal)
41-67% normal (equivocal)
<41% normal (abnormal)


C1Q Binding Assay

Reference Values:
C1Q Binding Assay 0.0 - 3.9 ug Eq/mL

Less than or equal to 3.9 ug Eq/mL is considered negative for circulating complement binding immune complexes.

Circulating immune complexes may be found without any evident pathology and positive results do not necessarily implicate the immune complex in a disease process.
**C1q Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (or mannan binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex. The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1-C4) result in an inability to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Inherited deficiency of C1 is rare. C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus [SLE], polymyositis, glomerulonephritis, and Henoch-Schönlein purpura), and SLE is the most common manifestation of C1 deficiency. The SLE associated with C1 deficiency is similar to SLE without complement deficiency, but the age of onset is often prior to puberty. Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton and common variable hypogammaglobulinemia and severe combined immunodeficiency), and this is most likely due to increased catabolism. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of first component of complement (C1) deficiency Investigation of a patient with an absent total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). The measurement of C1q activity is an indicator of the amount of first component of complement (C1) present. Absent C1q levels in the presence of normal C3 and C4 values are consistent with a C1 deficiency. Low C1q levels in the presence of normal C4 but normal C3 may indicate the presence of an acquired inhibitor (autoantibody) to C1 esterase inhibitor.

**Reference Values:**

34-63 U/mL


**C2 Complement, Functional, Serum**

**Clinical Information:** The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. This activation process results in the formation of the lytic membrane attack complex, as well as the generation of activation...
peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The absence of early components (C1, C2, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophoderma, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement (CH50) of nearly zero, with normal values for C3 and C4.

**Useful For:** Investigation of a patient with a low (absent) hemolytic complement (CH50)

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

**Reference Values:**
25-47 U/mL

**Clinical References:**

**C2 Complement, Functional, with Reflex, Serum**

**Clinical Information:** The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. This activation process results in the formation of the lytic membrane attack complex, as well as the generation of activation peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The absence of early components (C1, C2, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, and complement deficiency may be an etiologic factor in the development of autoimmune disease. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophoderma, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement (CH50) of nearly zero, with normal values for C3 and C4.

**Useful For:** Investigation of a patient with a low (absent) hemolytic complement (CH50), with reflex
testing to C3 and C4, if appropriate

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

**Reference Values:**
25-47 U/mL

**Clinical References:**

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C3 Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. C3 is at the entry point for all 3 activation pathways to activate the MAC. C3 deficiency may result in pneumococcal and neisserial infections as well as autoimmune diseases such as glomerulonephritis. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C3 / Complement C3, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C3 deficiency Investigation of a patient with undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C3 levels in the presence of other normal complement values are consistent with a C3 deficiency.

**Reference Values:**
21-50 U/mL

**Clinical References:**
C3a Level By RIA

Reference Values:
0-780 ng/mL

C4 Acylcarnitine, Quantitative, Urine

Clinical Information: An isolated elevation of iso-/butyrylcarnitine (C4) in plasma or newborn screening blood spots is related to a diagnosis of either short chain acyl-CoA dehydrogenase (SCAD) deficiency or isobutyryl-CoA dehydrogenase (IBD) deficiency. Diagnostic testing, including the evaluation of C4 excretion in urine, is necessary to differentiate the 2 clinical entities. Patients with IBD deficiency excrete an abnormal amount of C4 acylcarnitine in urine, whereas patients with SCAD deficiency can have a normal excretion of this metabolite. See Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevation) in Special Instructions for additional Information.

Useful For: Evaluation of patients with abnormal newborn screens showing elevations of iso-/butyrylcarnitine (C4) to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies

Interpretation: Almost all patients with isobutyryl-CoA dehydrogenase deficiency excrete an abnormal amount of iso-/butyrylcarnitine (C4) in their urine. Some, but not all, affected individuals also excrete elevated levels of isobutyrylglycine. Conversely, patients with short-chain acyl-CoA dehydrogenase deficiency can have a normal excretion of C4.

Reference Values:
<3.00 millimoles/mole creatinine


C4 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary clear immune complexes and to attract neutrophils or to generate to lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Approximately 20 cases of C4 deficiency have been reported. Most of these patients have systemic lupus erythematosus (SLE) or glomerulonephritis. Patients with C4 deficiency may also have frequent bacterial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C4 / Complement C4, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.
Useful For: Diagnosis of C4 deficiency Investigation of a patient with an undetectable total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent component 4 (C4) levels in the presence of normal C3 and C2 values are consistent with a C4 deficiency. Normal results indicate both normal C4 protein levels and normal functional activity. In hereditary angioedema, a disorder caused by C1 esterase inhibitor deficiency, absent or low C4 and C2 values are seen in the presence of normal C3 (due to activation and consumption of C4 and C2).

Reference Values: 22-45 U/mL


C4 Level by RIA

Reference Values: 0 - 2830 ng/mL

C5 Complement, Antigen, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an absent total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggests complement consumption. A small number of cases have been described in which the complement protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency C5FX / C5 Complement, Functional, Serum).

Reference Values: 10.6-26.3 mg/dL


C5FX
Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC and may have increased susceptibility to neisserial infections. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C5AG / C5 Complement, Antigen, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an undetectable total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent component 5 (C5) levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggest complement consumption. Normal results indicate both normal C5 protein levels and normal functional activity.

Reference Values: 29-53 U/mL


C5DCU
Clinical Information: An isolated elevation of glutarylcarnitine (C5-DC) in plasma or newborn screening blood spots is related to a diagnosis of glutaric aciduria type 1 (GA-1), also known as glutaric acidemia type 1. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase. Urinary excretion of C5-DC is a specific biochemical marker of GA-1 that appears to be elevated even in low excretors, those patients who are affected but have normal levels of glutaric acid in urine. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by
illness. Many affected individuals also have macrocephaly. Dietary treatment and aggressive interventions during time of illness are recommended to try to prevent or minimize neurologic injury, which is most likely to occur in infancy and early childhood. Prevalence is approximately 1 in 100,000 individuals. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see the Practice Resources: ACT Sheets and Algorithms at http://www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of C5-DC

**Diagnosis of glutaric aciduria type 1 deficiency**

**Interpretation:** Elevated excretion of C5-DC is a specific biochemical marker of glutaric aciduria type 1 that is elevated in affected patients, apparently even in low excretors or those affected individuals with normal levels of glutaric acid in urine.

**Reference Values:**

<1.54 millimoles/mole creatinine

**Clinical References:** Kolker S, Christensen E, Leonar JV, et al: Diagnosis and management of glutaric aciduria type I-revised recommendations. J Inherit Metab Dis. 2011:34:677-694

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**C5-OH Acylcarnitine, Quantitative, Urine**

**Clinical Information:** The differential diagnosis of an isolated elevation of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) in plasma or (newborn screening) blood spots includes the following disorders: -3-Methylcrotonyl-CoA carboxylase deficiency (common name: 3-methylcrotonylglycinuria), either infantile or maternal -3-Hydroxy 3-methylglutaryl-CoA lyase deficiency -Beta-ketothiolase deficiency -2-Methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency -3-methylglutaconic aciduria type I -Biotinidase deficiency -Holocarboxylase deficiency Confirmatory and diagnostic testing are necessary to differentiate these clinical entities. This test can be used to differentiate patients with 3-methylcrotonylglycinuria and with 3-methylglutaconic aciduria as they typically excrete larger amounts of C5-OH in urine compared to patients with the other diagnoses. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had positive newborn screening results. For more information, see the Practice Resources: ACT Sheets and Algorithms at http://www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of 3-hydroxyisovaleryl-/2-methyl-3-hydroxybutyryl-carnitine (C5-OH)

**Interpretation:** Preliminary data showed that an elevated excretion in urine and concentration in plasma of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) can be the only biochemical abnormalities in patients with 3-methylcrotonylglycinuria.

**Reference Values:**

<2.93 millimoles/mole creatinine


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**C6 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the
complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. A number of patients with C6 deficiency have been reported, and the majority of these patients are South African. Most of these patients have systemic meningococcal infection and some have had invasive gonococcal infections. Normal levels of C6 antigen have been reported in patients with dysfunctional C6 lytic activity.

**Useful For:** Diagnosis of C6 deficiency Investigation of a patient with an undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent component 6 (C6) levels in the presence of normal C3 and C4 values are consistent with a C6 deficiency. Absent C6 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C6 protein levels and normal functional activity.

**Reference Values:**
32-57 U/mL

**Clinical References:**

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**C7FX**

**C7 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. The majority of cases of C7 deficiency have neisserial infections, but cases of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, and pyoderma gangrenosum have been reported. The pathogenesis of the rheumatic disease is not clear. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C7 deficiency Investigation of a patient with an undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent component 7 (C7) levels in the presence of normal C3 and C4 values are consistent with a C7 deficiency. Absent C7 levels in the presence of low C3 and C4 values suggest complement consumption.

**Reference Values:**
36-60 U/mL

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
C8 Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Most patients with C8 deficiency have invasive neisserial infections. For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C8 deficiency Investigation of a patient with an undetectable total hemolytic complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent component 8 (C8) levels in the presence of normal C3 and C4 values are consistent with a C8 deficiency. Absent C8 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C8 protein levels and normal functional activity.

**Reference Values:**
33-58 U/mL


C9 Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the
complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. C9 deficiency is common in the Japanese population and has been reported to occur in almost 1% of the population. The lytic activity of C9-deficient serum is decreased. However, the assembly of C5b-C8 complexes will result in a transmembrane channel with lytic activity, although the lytic activity is reduced. Many C9-deficient patients are therefore asymptomatic. C9-deficient patients may, however, present with invasive neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C9 deficiency Investigation of a patient with a low total (hemolytic) complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent component 9 (C9) levels in the presence of normal C3 and C4 values are consistent with a C9 deficiency. Absent C9 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C9 protein levels and normal functional activity.

**Reference Values:**
37-61 U/mL

**Clinical References:**

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**C9ORF35377**

**C9orf72 Hexanucleotide Repeat, Molecular Analysis, Varies**

**Clinical Information:** Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting the upper and lower motor neurons. The disease is characterized by progressive spasticity, muscle wasting and paralysis, typically leading to death from respiratory failure. Frontotemporal dementia (FTD) is a dementia syndrome that predominantly involves the frontal and temporal lobes of the brain. Clinical presentation is variable and includes progressive changes in behavior and personality and language disturbances. Affected individuals may also exhibit extrapyramidal signs. ALS and FTD are now thought to represent an overlapping spectrum of disease. Recent literature has found that approximately 40% of familial ALS, 25% of familial FTD, and 90% of familial ALS/FTD cases have a large hexanucleotide repeat (GGGGCC) expansion in a noncoding region of C9orf72. At lower frequency, C9orf72 hexanucleotide repeat expansions have also been observed in individuals with sporadic ALS, FTD, and ALS/FTD. The vast majority of individuals affected with a C9orf72-related disorder (c9ALS, c9FTD, or c9ALS/FTD) have hexanucleotide repeat expansions in the hundreds to thousands, while unaffected individuals have repeat sizes less than 20. The significance of repeat sizes between 20 and 100 repeats is currently unclear as both healthy controls and individuals with ALS and/or FTD phenotypes have been reported with repeat sizes in this range.

**Useful For:** Molecular confirmation of clinically suspected cases of c9FTD/ALS, frontotemporal dementia (FTD), or amyotrophic lateral sclerosis (ALS) Presymptomatic testing for individuals with a family history of c9FTD/ALS and a documented expansion in the C9orf72 gene

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


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

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

**Useful For:** Establishing a diagnosis of an allergy to cabbage Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<td>Strongly positive</td>
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</tbody>
</table>

Reference values apply to all ages.


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**Cadmium for Occupational Monitoring, Blood**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Tobacco smoke is another common source of cadmium exposure.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal

**Interpretation:** Normal blood cadmium is <5.0 mcg/L, with most results in the range of 0.5 to 2.0 mcg/L. Acute toxicity will be observed when the blood level exceeds 50 mcg/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-4.9 mcg/L</td>
<td>Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Cadmium Occupational Exposure, Random, Urine**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke.
smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting occupational exposure to cadmium in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure

**Reference Values:**
Only orderable as part of profile. See CDUO / Cadmium Occupational Exposure, Random, Urine or HMSOR / Heavy Metals Occupational Exposure with Reflex, Urine.


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**CDOU 608892**

**Cadmium Occupational Exposure, Random, Urine**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting occupational exposure to cadmium in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure

**Reference Values:**
Only orderable as part of profile. For more information see:
- CDUOE / Cadmium Occupational Exposure, Random, Urine
- HMSOR / Heavy Metal Occupational Exposure, with Reflex, Random, Urine

Cadmium Occupational Exposure, Random, Urine

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting occupational exposure to cadmium, a toxic heavy metal in random urine specimens

**Interpretation:** Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration (OSHA) cadmium standard is below 3.0 mcg/g creatine and the biological exposure index is 5 mcg/g creatinine.

**Reference Values:**
Biological Exposure Indices (BEI): <5.0 mcg/g creatinine

**Clinical References:**
potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in some patients exposed to cadmium. See also CDUOE / Cadmium, Occupational Exposure, Random, Urine. If employees are being monitored in the workplace, the Occupational Safety and Health Administration (OSHA) requires that laboratory reports express the cadmium excretion rate per gram of creatinine rather than per 24 hours. This alternative test is available to accommodate that requirement. Mayo Clinic Laboratories is certified to provide this test.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal in 24-hour urine specimens

**Interpretation:** Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration (OSHA) cadmium standard is less than 3.0 mcg/g creatine and the biological exposure index is 5 mcg/g creatinine.

**Reference Values:**
- 0-17 years: not established
- > or =18 years: <0.7 mcg/24 hour

**Clinical References:**

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**Cadmium, Blood**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal

**Interpretation:** Normal blood cadmium is <5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL.

**Reference Values:**
- <5.0 ng/mL
  - Reference values apply to all ages.

**Clinical References:**
Cadmium/Creatinine Ratio, Random, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

Useful For: Detecting exposure to cadmium, a toxic heavy metal, using random urine specimens

Interpretation: Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration (OSHA) cadmium standard is less than 3.0 mcg/g creatine and the biological exposure index is 5 mcg/g creatinine.

Reference Values:
0-17 years: not established
> or =18 years: <0.6 mcg/g creatinine


Cadmium/Creatinine Ratio, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the
results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting exposure to cadmium, in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure.

**Reference Values:**
Only orderable as part of profile. See CDRCR / Cadmium/Creatinine Ratio, Random, Urine or HMCRU / Heavy Metal/Creatinine Ratio, with Reflex, Urine.

**Clinical References:**

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**Cadmium/Creatinine Ratio, Urine**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting exposure to cadmium using random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure.

**Reference Values:**
Only orderable as part of profile. For more information, see:
- CDUCR / Cadmium/Creatinine Ratio, Random, Urine
- HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

**Clinical References:**
Caffeine, Serum

Clinical Information: Caffeine is used to treat apnea of prematurity that occurs in newborn infants, the most frequent complication seen in the neonatal nursery. In neonates, caffeine has a half-life that ranges from approximately 3 to 4 days, which is much longer than in adults (typically 4-6 hours) due to the immaturity of the neonatal liver. This requires that small doses be administered at much longer intervals than would be predicted based on adult pharmacokinetics. The volume of distribution of caffeine is 0.8-0.9 L/kg (infants) or 0.6 L/kg (adults) and the drug is approximately 36% protein bound. Toxicity observed in neonates is characterized by central nervous system and skeletal muscle stimulation and bradycardia. These symptoms are seen in adults at lower levels than in neonates, suggesting that neonates have much greater tolerance to the drug.

Useful For: Monitoring caffeine therapy in neonates Assessing caffeine toxicity in neonates

Interpretation: Optimal pharmacologic response occurs when the serum level is in the range of 8.0 to 20.0 mcg/mL. Toxicity in neonates and adults may be seen when the serum level is above 20.0 mcg/mL.

Reference Values:
Therapeutic: 8.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL


Calcitonin (CALCI) Immunostain, Technical Component Only

Clinical Information: Calcitonin is a hormone involved in calcium metabolism. Staining for calcitonin produces fine granular, cytoplasmic staining of C cells of thyroid, medullary thyroid carcinomas, many atypical laryngeal carcinoids, and other neuroendocrine tumors. Amyloid deposits within medullary thyroid carcinoma may also exhibit varying degrees of calcitonin immunoreactivity.

Useful For: Aids in the identification of C cells of thyroid, medullary thyroid carcinomas, many atypical laryngeal carcinoids, and other neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Calcitonin, Fine-Needle Aspiration Biopsy Needle Wash, Lymph Node

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
Clinical Information: Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C-cells) of the thyroid gland. Malignant tumors arising from thyroid C-cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising less than 5% of all thyroid malignancies. Measurement of serum calcitonin is used in the follow-up of patients who underwent surgical removal of the thyroid gland. Studies have reported that the measurement of calcitonin in fine-needle aspiration biopsy (FNAB)-needle washes improves the evaluation of suspicious lymph nodes in patients with a history of MTC when used in combination with cytology. Comparing the results of calcitonin in the needle rinse with serum calcitonin is highly recommended. An elevated calcitonin in the serum could falsely elevate calcitonin in the washings, if the rinse is contaminated with blood. In these cases, only calcitonin values significantly higher than the serum should be considered as true-positives. Cytologic examination and measurement of calcitonin can be performed on the same specimen. To measure calcitonin, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination (for a smear or CytoTrap preparation) has been expelled from the needle. Calcitonin levels are measured in the needle wash.

Useful For: As an adjunct to cytologic examination of fine-needle aspiration specimens in athyrotic individuals treated for medullary thyroid carcinoma to confirm or exclude metastases in enlarged or ultrasonographically suspicious lymph nodes

Interpretation: In athyrotic patients with a history of medullary thyroid carcinoma (MTC), a fine-needle aspiration calcitonin value of 5.0 pg/mL and greater is suggestive of the presence of metastatic MTC in the biopsied lymph node. Calcitonin values less than 5.0 pg/mL suggest the lymph node does not contain medullary thyroid carcinoma. This result is dependent on accurate sampling and a total needle wash volume between 0.5 to 1.5 mL. This test should be interpreted in the context of the clinical presentation, imaging, and cytology findings. If the results are discordant with the clinical presentation, a sampling error at the time of biopsy should be considered.

Reference Values: An interpretive report will be provided.


Calcitonin, Serum

Clinical Information: Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C-cells) of the thyroid gland. The main action of calcitonin is the inhibition of bone resorption by regulating the number and activity of osteoclasts. Calcitonin is secreted in direct response to serum hypercalcemia and may prevent large oscillations in serum calcium levels and excessive loss of body calcium. However, in comparison to parathyroid hormone and 1,25-dihydroxyvitamin D, the role of calcitonin in the regulation of serum calcium in humans is minor. Measurements of serum calcitonin levels are, therefore, not useful in the diagnosis of disorders of calcium homeostasis. Malignant tumors arising from thyroid C cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising less than 5% of all thyroid malignancies. Approximately 25% of these are familial cases, usually appearing as a component of multiple endocrine neoplasia type II (MENII, Sipple syndrome). MTC may also occur in families without other associated endocrine dysfunction, with similar autosomal dominant transmission as MENII, which is then called familial medullary thyroid carcinoma (FMTC). Variants in the RET proto-oncogene are associated with MENII and FMTC. Serum calcitonin concentrations are high in infants, decline rapidly, and are relatively stable from childhood through adult life. In general, calcitonin
serum concentrations are higher in men than in women due to the larger C-cell mass in men. Serum calcitonin concentrations may be increased in patients with chronic renal failure, and other conditions such as hyperparathyroidism, leukemic and myeloproliferative disorders, Zollinger-Ellison syndrome, autoimmune thyroiditis, small cell and large cell lung cancers, breast and prostate cancer, mastocytosis, and various neuroendocrine tumors, in particular, islet cell tumors.

**Useful For:** Aids in the diagnosis and follow-up of medullary thyroid carcinoma Aids in the evaluation of multiple endocrine neoplasia type II and familial medullary thyroid carcinoma This test is not useful for evaluating calcium metabolic diseases.

**Interpretation:** Although most patients with sporadic medullary thyroid carcinoma (MTC) have high basal serum calcitonin concentrations, 30% of those with familial MTC or multiple endocrine neoplasia type II (MENII) have normal basal levels. In completely cured cases following surgical therapy for MTC, serum calcitonin levels fall into the undetectable range over a variable period of several weeks. Persistently elevated postoperative serum calcitonin levels usually indicate incomplete cure. The reasons for this can be locoregional lymph node spread or distant metastases. In most of these cases, imaging procedures are required for further workup. Those individuals who are then found to suffer only locoregional spread may benefit from additional surgical procedures. However, the survival benefits derived from such approaches are still debated. A rise in previously undetectable or very low postoperative serum calcitonin levels is highly suggestive of disease recurrence or spread, and should trigger further diagnostic evaluations.

**Reference Values:**

**Pediatric**
- 1 month: < or =34 pg/mL
- 2 months: < or =31 pg/mL
- 3 months: < or =28 pg/mL
- 4 months: < or =26 pg/mL
- 5 months: < or =24 pg/mL
- 6 months: < or =22 pg/mL
- 7 months: < or =20 pg/mL
- 8 months: < or =19.0 pg/mL
- 9 months: < or =17.0 pg/mL
- 10 months: < or =16.0 pg/mL
- 11 months: < or =15.0 pg/mL
- 12-14 months: < or =14.0 pg/mL
- 15-17 months: < or =12.0 pg/mL
- 18-20 months: < or =10.0 pg/mL
- 21-23 months: < or =9.0 pg/mL
- 2 years: < or =8.0 pg/mL
- 3-9 years: < or =7.0 pg/mL
- 10-15 years: < or =6.0 pg/mL
- 16 years: < or =5.0 pg/mL

**Adults**
17 years and older:
- Males: < or =14.3 pg/mL
- Females: < or =7.6 pg/mL

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

**Clinical References:**
**Calcium, 24 Hour, Urine**

**Clinical Information:** Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

**Useful For:** Evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturation Evaluation of bone diseases, including osteoporosis and osteomalacia

**Interpretation:** Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed idiopathic). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is above 250 mg in men and above 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

**Reference Values:**
Males: <250 mg/24 hours*
Females: <200 mg/24 hours*
*Values represent clinical cutoffs above which studies have demonstrated increased risk of kidney stone formation. These values were not determined in a reference range study.

Reference values have not been established for patients who are less than 18 years of age.
Reference values apply to 24-hour collection.

**Clinical References:**

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**Calcium, Ionized, Serum**

**Clinical Information:** Ionized calcium, which accounts for 50% to 55% of total calcium, is the physiologically active form of calcium. Low ionized calcium values are often seen in renal disease, critically ill patients, or patients receiving rapid transfusion of citrated whole blood or blood products. Increased serum ionized calcium concentrations may be seen with primary hyperparathyroidism, ectopic parathyroid hormone-producing tumors, excess intake of vitamin D, or various malignancies. Nomograms have been used to calculate ionized calcium from total calcium, albumin, and pH values. However, calculated ionized calcium results have proven to be unsatisfactory. A Mayo study of 114 patients found significant differences between ionized and total calcium in 26% of patients.

**Useful For:** Assessing calcium states during liver transplantation surgery, cardiopulmonary bypass, or any procedure requiring rapid transfusion of whole blood in neonates and critically ill patients

Second-order test in the evaluation of patients with abnormal calcium values
**Interpretation:** Serum ionized calcium concentrations 50% below normal will result in severely reduced cardiac stroke work. With moderate to severe hypocalcemia, left ventricular function may be profoundly depressed. Ionized calcium values are higher in children and young adults. Ionized calcium result has been adjusted to pH 7.40 to account for changes in specimen pH that may occur during transport. Ionized calcium concentration increases approximately 0.2 mg/dL per 0.1 pH unit decrease.

**Reference Values:**

**IONIZED CALCIUM**
- < or =13 days old: not established
- 14 days-<1 year: 5.21-5.99 mg/dL
- 1-<2 years: 5.04-5.84 mg/dL
- 2-<3 years: 4.87-5.67 mg/dL
- 3-<24 years: 4.83-5.52 mg/dL
- 24-< or =97 years: 4.57-5.43 mg/dL
- > or =98 years: not established

**pH**
- < or =13 days old: not established
- 14 days-97 years old: 7.35-7.48
- > or =98 years old: not established

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


**CACR2 610644 Calcium, Random, Urine**

**Clinical Information:** Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

**Useful For:** Evaluation of calcium oxalate and calcium phosphate kidney stone risk in a random urine collection Calculation of urinary supersaturation Evaluation of bone diseases, including osteoporosis and osteomalacia

**Interpretation:** Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed idiopathic). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile,
Calcium, Random, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Measurement of calcium for the evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturations Evaluation of bone diseases, including osteoporosis and osteomalacia

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values:
Only orderable as part of a profile. For more information see CACR3 / Calcium/Creatinine Ratio, Random, Urine

1 month-<12 months: 0.03-0.81 mg/mg creat
12 months-<24 months: 0.03-0.56 mg/mg creat
24 months-<3 years: 0.02-0.50 mg/mg creat
3 years-<5 years: 0.02-0.41 mg/mg creat
5 years-<7 years: 0.01-0.30 mg/mg creat
7 years-<10 years: 0.01-0.25 mg/mg creat
10 years-<18 years: 0.01-0.24 mg/mg creat
18 years-83 years: 0.05-0.27 mg/mg creat
Reference values have not been established for patients who are less than 1 month of age.
Reference values have not been established for patients who are greater than 83 years of age.

3 years-<5 years: 0.02-0.41 mg/mg creat
5 years-<7 years: 0.01-0.30 mg/mg creat
7 years-<10 years: 0.01-0.25 mg/mg creat
10 years-<18 years: 0.01-0.24 mg/mg creat
18 years-83 years: 0.05-0.27 mg/mg creat
Reference values have not been established for patients who are less than 1 month of age.
Reference values have not been established for patients who are greater than 83 years of age.


Calcium, Total, Serum

Clinical Information: The calcium content of an adult is somewhat over 1 kg (about 2% of the body weight). Of this, 99% is present as calcium hydroxyapatite in bones and less than 1% is present in the extra-osseous intracellular space or extracellular space (ECS). The calcium level in the ECS is in dynamic equilibrium with the rapidly exchangeable fraction of bone calcium. In serum, calcium is bound to a considerable extent to proteins (approximately 40%), 10% is in the form of inorganic complexes, and 50% is present as free or ionized calcium. Calcium ions affect the contractility of the heart and the skeletal musculature, and are essential for the function of the nervous system. In addition, calcium ions play an important role in blood clotting and bone mineralization. Hypocalcemia is due to the absence or impaired function of the parathyroid glands or impaired vitamin-D synthesis. Chronic renal failure is also frequently associated with hypocalcemia due to decreased vitamin-D synthesis as well as hyperphosphatemia and skeletal resistance to the action of parathyroid hormone (PTH). Characteristic symptoms of hypocalcemia are latent or manifest tetany and osteomalacia. Hypercalcemia is brought about by increased mobilization of calcium from the skeletal system or increased intestinal absorption. A majority of cases are due to primary hyperparathyroidism (pHPT) or bone metastasis of carcinoma of the breast, prostate, thyroid gland, or lung. Patients who have pHPT and bone disease, renal stones or nephrocalcinosis, or other signs or symptoms are candidates for surgical removal of the parathyroid glands. Severe hypercalcemia may result in cardiac arrhythmia. Calcium levels may also reflect abnormal vitamin D or protein levels.

Useful For: Diagnosis and monitoring of a wide range of disorders including diseases of bone, kidney, parathyroid gland, or gastrointestinal tract

Interpretation: Hypocalcemia: Long-term therapy must be tailored to the specific disease causing the hypocalcemia. The therapeutic endpoint is to achieve a serum calcium level of 8.0 to 8.5 mg/dL to prevent tetany. For symptomatic hypocalcemia, calcium may be administered intravenously. Hypercalcemia: The level at which hypercalcemic symptoms occur varies from patient to patient. Symptoms are common when serum calcium levels are above 11.5 mg/dL, although patients may be asymptomatic at this level. Levels above 12.0 mg/dL are considered a critical value. Severe hypercalcemia (>15.0 mg/dL) is a medical emergency.

Reference Values:
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
> or =60 years: 8.8-10.2 mg/dL

Calcium/Creatinine Ratio, Random, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Calculation of calcium concentration per creatinine concentration

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values: Only orderable as part of a profile. For more information see CACR3 / Calcium/Creatinine Ratio, Random, Urine

1 month-<12 months: 0.03-0.81 mg/mg creat
12 months-<24 months: 0.03-0.56 mg/mg creat
24 months-<3 years: 0.02-0.50 mg/mg creat
3 years-<5 years: 0.02-0.41 mg/mg creat
5 years-<7 years: 0.01-0.30 mg/mg creat
7 years-<10 years: 0.01-0.25 mg/mg creat
10 years-<18 years: 0.01-0.24 mg/mg creat
18 years-83 years: 0.05-0.27 mg/mg creat

Reference values have not been established for patients who are less than 1 month of age. Reference values have not been established for patients who are greater than 83 years of age.

**CACR3**

**610594 Calcium/Creatinine Ratio, Random, Urine**

**Clinical Information:** Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

**Useful For:** Evaluation of calcium oxalate and calcium phosphate kidney stone risk. Calculation of urinary supersaturation. Evaluation of bone diseases, including osteoporosis and osteomalacia.

**Interpretation:** Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed “idiopathic”). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

**Reference Values:**

- 1 month-<12 months: 0.03-0.81 mg/mg creat
- 12 months-<24 months: 0.03-0.56 mg/mg creat
- 24 months-<3 years: 0.02-0.50 mg/mg creat
- 3 years-<5 years: 0.02-0.41 mg/mg creat
- 5 years-<7 years: 0.01-0.30 mg/mg creat
- 7 years-<10 years: 0.01-0.25 mg/mg creat
- 10 years-<18 years: 0.01-0.24 mg/mg creat
- 18 years-83 years: 0.05-0.27 mg/mg creat

Reference values have not been established for patients who are less than 1 month of age. Reference values have not been established for patients who are greater than 83 years of age.

**Clinical References:**

**CALD**

**70369 Caldesmon Immunostain, Technical Component Only**

**Clinical Information:** Caldesmon is a smooth muscle specific protein that regulates smooth muscle contraction. This clone recognizes the high-molecular-weight variant (h-caldesmon) and does not react with the nonmuscle variant. Neither variant of caldesmon is present in skeletal muscle. Anti-h-caldesmon seems to be a reliable marker of smooth muscle differentiation, and may assist in the diagnosis of smooth muscle tumors.

**Useful For:** A marker of smooth muscle differentiation.
Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CAVPC 83900

California Virus (La Crosse) Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: California (La Crosse) virus is a member of the Bunyaviridae family and it is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children less than 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children and almost always in patients who have had seizures during the acute illness. An estimated 2% of patients have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (<2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. Serious California (La Crosse) virus infections primarily involve children, especially boys. Adult males exposed to California viruses have high prevalence rates of antibody but usually show no serious illness. Infection among males is primarily due to working conditions and sports activities taking place where the vector is present.

Useful For: Aiding in the diagnosis of California (La Crosse) encephalitis using spinal fluid specimens

Interpretation: A positive result indicates intrathecal synthesis of antibody and is indicative of neurological infection.

Reference Values:
IgG: <1:1
IgM: <1:1
Reference values apply to all ages.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
California Virus (La Crosse) IgG and IgM, Serum

**Clinical Information:** California virus (La Crosse) is a member of the Bunyaviridae family and is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children under 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paralytic. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. Serious California (La Crosse) virus infections primarily involve children, especially boys. Adult males exposed to California viruses have high prevalence rates of antibody but usually show no serious illness. Infection among males is primarily due to working conditions and sports activities taking place where the vector is present.

**Useful For:** Aiding the diagnosis of California virus (La Crosse)

**Interpretation:** In patients infected with these or related viruses, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG of 1:10 or greater indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:**
**Clinical Information:** Calmodulin-binding transcription activator 1 (CAMTA1) protein overexpression in the nucleus is the result of the WWTR1-CAMTA1 gene fusion, which is found in approximately 90% of epithelioid hemangioendotheliomas (EHE). CAMTA1 can be used to distinguish EHE from other tumors with epithelioid morphology.

**Useful For:** Aids in the diagnosis of epithelioid hemangioendotheliomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**CALPN**

**Calponin Immunostain, Technical Component Only**

**Clinical Information:** Calponin is a cytoskeleton-associated protein that can bind to actin, tropomyosin, troponin C, and calmodulin and is involved in modulation of smooth muscle contraction. Calponin expression has been demonstrated in smooth muscle cells of blood vessels and myoepithelial cells in the lobules, ducts, and galactophorous sinuses of normal human breast.

**Useful For:** Marker for myoepithelium when differentiating ductal carcinomas in situ from infiltrating breast carcinoma Characterization of tumors of smooth muscle or myoepithelial lineage

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**CALPR**

**Calprotectin, Feces**

**Clinical Information:** Calprotectin, formed as a heterodimer of S100A8 and S100A9, is a member of the S100 calcium-binding protein family. It is expressed primarily by granulocytes and, to a lesser degree, by monocytes/macrophages and epithelial cells. In neutrophils, calprotectin comprises almost 60% of the total cytoplasmic protein content. Activation of the intestinal immune system leads to recruitment of cells from the innate immune system, including neutrophils. The neutrophils are then activated, which leads to
release of cellular proteins, including calprotectin. Calprotectin is eventually translocated across the epithelial barrier and enters the lumen of the gut. As the inflammatory process progresses, the released calprotectin is absorbed by fecal material before it is excreted from the body. The amount of calprotectin present in the feces is proportional to the number of neutrophils within the gastrointestinal mucosa and can be used as an indirect marker of intestinal inflammation. Calprotectin is most frequently used as part of the diagnostic evaluation of patients with suspected inflammatory bowel disease (IBD). Patients with IBD may be diagnosed with Crohn disease or ulcerative colitis. Although distinct in their pathology and clinical manifestations, both are associated with significant intestinal inflammation. Elevated concentrations of fecal calprotectin may be useful in distinguishing IBD from functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). When used for this differential diagnosis, fecal calprotectin has sensitivity and specificity both of approximately 85%. However, it must be remembered that increases in fecal calprotectin are not diagnostic for IBD, as other disorders such as celiac disease, colorectal cancer, and gastrointestinal infections, may also be associated with neutrophilic inflammation.

**Useful For:** Evaluation of patients suspected of having a gastrointestinal inflammatory process

**Interpretation:** Calprotectin concentrations of 50.0 mcg/g and lower are not suggestive of an active inflammatory process within the gastrointestinal system. For patients experiencing gastrointestinal symptoms, consider further evaluation for functional gastrointestinal disorders. Calprotectin concentrations between 50.1 and 120.0 mcg/g are borderline and may represent a mild inflammatory process, such as in treated inflammatory bowel disease (IBD) or associated with nonsteroidal anti-inflammatory drug (NSAID) or aspirin usage. For patients with clinical symptoms suggestive of IBD, retesting in 4 to 6 weeks may be indicated. Calprotectin concentrations of 120.1 mcg/g and higher are suggestive of an active inflammatory process within the gastrointestinal system. Further diagnostic testing to determine the etiology of the inflammation is suggested.

**Reference Values:**
- < or =50.0 mcg/g (Normal)
- 50.1-120.0 mcg/g (Borderline)
- > or =120.1 mcg/g (Abnormal)

**Clinical References:**

**CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Reflex, Varies**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia.
and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluates for mutations in CALR in an algorithmic process for the MPN / Myeloproliferative Neoplasm (MPN), JAK2 V617F with Reflex to CALR and MPL

**Interpretation:** An interpretation will be provided under the MPN / Myeloproliferative Neoplasm (MPN), JAK2 V617F with Reflex to CALR and MPL.

**Reference Values:** Only orderable as a reflex. For more information see MPN / Myeloproliferative Neoplasm (MPN), JAK2 V617F with Reflex to CALR and MPL.

An interpretive report will be provided.

**CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Varies**

**Clinical Information:** The most frequent genetic mutation in BCR-ABL1-negative myeloproliferative neoplasm (MPN), essential thrombocythemia (ET), and primary myelofibrosis (PMF) is the JAK2V617F mutation, which is present in approximately 50% to 60% of patients. It serves as a confirmatory molecular marker of these diseases. Mutations in the MPL gene are found in an additional 5% to 10% of ET and PMF cases. It was recently discovered that somatic mutation (insertions and deletions) in exon 9 of the CALR gene is the second most frequent somatic mutation after JAK2 in ET and PMF patients, and it is mutually exclusive of JAK2 and MPL mutations.(1,2) It has a frequency of approximately 49% to 88% in JAK2 and MPL-wild type (WT) ET and PMF, and is not found in polycythemia vera (PV) patients.(1-4) Therefore, CALR mutation serves as an important diagnostic molecular marker in ET and PMF. The CALR gene encodes for calreticulin, a multifunctional protein with a C-terminus rich in acidic amino acids and a KDEL ER-retention motif. All the pathologic CALR mutations reported to date are out-of-frame insertion and/or deletions (indel) in exon 9, generating a 1 base-pair (bp) frame shift and a mutant protein with a novel C-terminus rich in basic amino acids and loss of the KDEL ER-retention signal. The most common mutation types are 52-bp deletion (c.1092_1143del, L367fs*46) and 5-bp insertion (c.1154_1155insTTGCC, K385fs*47), and they comprise approximately 85% of CALR mutations in MPN. (1,2) CALR mutations have been found in hematopoietic stem and progenitor cells in MPN patients(2) and may activate the STAT5 signaling pathway.(1) They are associated with decreased risk of thrombosis in ET (1,3-5), and better survival in PMF compared to JAK2 mutations.(5)

**Useful For:** Rapid and sensitive detection of insertion and deletion-type mutations in exon 9 of CALR An aid in distinction between reactive thrombocytosis and leukocytosis versus a myeloproliferative neoplasm (MPN), especially essential thrombocythemia (ET) and primary myelofibrosis (PMF), and is highly informative in cases in which JAK2 and MPL testing are negative Especially helpful to the pathologist in those bone marrow cases with ambiguous etiology of thrombocytosis, equivocal bone marrow morphologic findings of MPN, and unexplained reticulin fibrosis An aid in prognostication of PMF and thrombosis risk assessment in ET

**Interpretation:** An interpretive report will be issued. The results will be reported as 1 of the 3 states if DNA amplification is successful (see Cautions): -Positive. A deletion/insertion-type mutation was detected in CALR, exon 9. -Negative. No deletion or insertion was detected in CALR, exon 9. -Equivocal. A small amplicon suspicious for a deletion/insertion type mutation was detected in CALR, exon 9. Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical
and other laboratory and morphologic features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplastic disorders.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

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**CALRC 71486 Calreticulin ex9mut Immunostain, Technical Component Only**

**Clinical Information:** The detection of calreticulin exon 9 frameshift alterations can assist in the diagnosis and prognostication of myeloproliferative diseases. Although these alterations are heterogeneous, they all result in a protein with a novel 36-amino acid C terminus the anticalreticulin CAL2 clone specifically identifies. Most patients with essential thrombocythemia or primary myelofibrosis not associated with Janus kinase 2 (JAK2) or MPL variants are associated with CALR exon 9 variants and primary myelofibrosis patients carrying CALR variants have a more indolent clinical course.

**Useful For:** Identifying the presence of CALR exon 9 frameshift alterations in myeloproliferative neoplasms

**Interpretation:** This test does not include pathologist interpretation; if an interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404.

**Clinical References:**

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**CALNN 70371 Calretinin Immunostain, Technical Component Only**

**Clinical Information:** Calretinin is expressed in benign and malignant mesothelial cells and strongly expressed in Leydig cells of the testis.

**Useful For:** Separating mesotheliomas from carcinomas, which usually lack expression of calretinin

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control
tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CAMPC 606218**

**Campylobacter Culture, Feces**

**Clinical Information:** Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Campylobacter enteritis is an important cause of acute diarrhea worldwide. The organism inhabits the intestinal tracts of a wide range of animal hosts, notably poultry; contamination from these sources can lead to foodborne disease that is typically caused by Campylobacter jejuni or Campylobacter coli. Campylobacter infection can also be transmitted via water-borne routes or direct contact with animals or animal products. Early symptoms (1–7 days after exposure) include abrupt onset of abdominal pain, diarrhea, and occasionally vomiting. The acute illness is characterized by cramping, abdominal pain, and diarrhea. Patients may report 10 or more bowel movements per day. Bloody feces may be observed. Diarrhea is typically self-limited, lasting around 7 days. Proper hydration is necessary. Antibiotics are not needed for most cases of Campylobacter gastroenteritis, except if patients experience severe disease or if they are immunocompromised.

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

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

**Reference Values:**
No growth of pathogen

**Clinical References:**

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**CFTH 82778**

**Canary Feathers, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to canary feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Canary Grass, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to canary grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</tbody>
</table>

Reference values apply to all ages.


**Canavan Disease, ASPA Mutation Analysis, Varies**

**Clinical Information:** Canavan disease is a severe leukodystrophy resulting from a deficiency of the enzyme aspartoacylase. Mutations in the ASPA gene cause the clinical manifestations of Canavan disease. The deficiency of aspartoacylase leads to spongy degeneration of the brain, and the disease is characterized by delayed development beginning at age 3 to 6 months, head lag, macrocephaly, and hypotonia. Death usually occurs within the first decade of life. The carrier rate in the Ashkenazi Jewish population is 1 in 41. Four ASPA mutations are included in this test: 433(-2)A->G, A305E, E285A, and Y231X. The E285A and Y231X mutations account for approximately 98% of the mutations in the Ashkenazi Jewish population. The A305E mutation accounts for approximately 50% of the mutations in the non-Ashkenazi Jewish population.

**Useful For:** Carrier testing for Canavan disease in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of Canavan disease in at-risk pregnancies Confirmation of a suspected clinical diagnosis of Canavan disease in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretative report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**Cancer Antigen 125 (CA 125), Serum**

**Clinical Information:** Cancer antigen 125 (CA 125) is a glycoprotein antigen normally expressed in tissues derived from coelomic epithelia (ovary, fallopian tube, peritoneum, pleura, pericardium, colon, kidney, stomach). Serum CA 125 is elevated in approximately 80% of women with advanced epithelial ovarian cancer, but assay sensitivity is suboptimal in early disease stages. The average reported sensitivities are 50% for stage I and 90% for stage II or greater. Elevated serum CA 125 levels have been reported in individuals with a variety of nonovarian malignancies including cervical, liver, pancreatic, lung, colon, stomach, biliary tract, uterine, fallopian tube, breast, and endometrial carcinomas. Elevated
serum CA 125 levels have been reported in individuals with a variety of benign conditions including: cirrhosis, hepatitis, endometriosis, first trimester pregnancy, ovarian cysts, and pelvic inflammatory disease. Elevated levels during the menstrual cycle also have been reported.

**Useful For:** Evaluating patients' response to ovarian cancer therapy Predicting recurrent ovarian cancer This test is not useful for cancer detection screening in the normal population.

**Interpretation:** In monitoring studies, elevations of cancer antigen 125 (CA 125) above the reference interval after debulking surgery and chemotherapy indicate that residual disease is likely (>95% accuracy). However, normal levels do not rule out recurrence. A persistently rising CA 125 value suggests progressive malignant disease and poor therapeutic response. Physiologic half-life of CA 125 is approximately 5 days. In patients with advanced disease who have undergone cytoreductive surgery and are on chemotherapy, a prolonged half-life (>20 days) may be associated with a shortened disease-free survival.

**Reference Values:**
Males: Not applicable
Females: <46 U/mL


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**CA153**

**Cancer Antigen 15-3 (CA 15-3), Serum**

**Clinical Information:** Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens, which are large molecular weight glycoproteins with O-linked oligosaccharide chains. Tumor-associated antigens encoded by the human MUC-1 gene are known by several names, including MAM6, milk mucin antigen, cancer antigen (CA) 27.29, and CA 15-3. CA 15-3 assay values are not elevated in most normal individuals and are frequently elevated in sera from breast cancer patients. Nonmammary malignancies in which elevated CA 15-3 assay values have been reported include: lung, colon, pancreas, primary liver, ovary, cervix, and endometrium.

**Useful For:** Managing breast cancer patients when used in conjunction with clinical information and other diagnostic procedures Serial testing to assist in early detection of disease recurrence in previously treated stage II and III breast cancer patients Monitoring response to therapy in metastatic breast cancer patients This test is not useful as a cancer screening test.

**Interpretation:** Increasing and decreasing values show correlation with disease progression and regression, respectively.(1) Increasing cancer antigen 15-3 (CA 15-3) assay values in patients at risk for breast cancer recurrence after primary therapy may be indicative of recurrent disease before it can be detected clinically (2,3) and may be used as an indication that additional tests or procedures should be performed.

**Reference Values:**
Males: <30 U/mL (use not defined)
Females: <30 U/mL

Concordance analysis of paired cancer antigen (CA) 15-3 and 27.29 testing. Breast Cancer Research and Treatment. 2018;167:269-276

**Cancer-Associated Retinopathy Panel (CARP) by Immunoblot and IHC**

**Reference Values:**
A final report will be provided.

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**Candida albicans (Monilia), IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Candida albicans (Monilia) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</tr>
</tbody>
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Reference values apply to all ages.

Clinical Information: Although there have been many publications concerning the measurement of allergen-specific IgG, the clinical utility of such tests has not been established except in special situations. Thus, the quantitative IgG test should only be ordered by specialists who recognize the limitations of the test. The normal reference ranges reported represent the expected results for individuals who have no unusual exposure and have not been immunized with the indicated allergen. The ranges reported have no disease-associated significance.

Reference Values: <52.0 mcg/mL

Candida auris Surveillance, Molecular Detection, PCR, Varies

Clinical Information: Candida auris is a yeast that was first identified as causing disease in an individual in Japan in 2009. Since then, cases have been reported in more than 30 countries worldwide. The first case of Candida auris in the US was reported in 2015, and cases have been reported in a number of states. In addition to causing disease, Candida auris can colonize individuals without signs or symptoms of disease. Candida auris can cause serious and sometimes fatal infections, is often resistant to one or more classes of antifungal drugs, and inappropriate treatment may occur as it can be misidentified in the laboratory. In addition, Candida auris appears to be more resistant to disinfection than other yeasts, leading to prolonged survival in the environment and increasing the possibility of transmission in hospitals and nursing homes. In December 2018, the Center for Disease Control and Prevention (CDC) recommended that health care facilities implement routine surveillance screening of patients who have had an overnight stay in a health care facility outside of the US over the past year, particularly if the hospitalization was in a country with confirmed cases of Candida auris. The CDC also recommended considering screening of patients who have been hospitalized outside of the US and have a documented infection or colonization with a carbapenamase-producing Gram-negative bacteria. These patients have frequently been found to have Candida auris colonization as well. A second group of people for whom screening is recommended includes health care workers who have been in close contact with patients who have previously unrecognized Candida auris infection or colonization. The Candida auris polymerase chain reaction (PCR) assay detects and identifies Candida auris from blood or urine specimens and also from swabs including combination groin/axilla surveillance swabs and nares surveillance swabs.

Useful For: Detection of Candida auris from surveillance swabs This test should not be used to determine cure or to monitor response to therapy.

Interpretation: A positive result indicates the presence of Candida auris DNA. A negative result indicates the absence of detectable Candida auris DNA. An inhibited result indicates that inhibitors are present in the specimen that could prevent the detection of C auris DNA. A new specimen can be resubmitted under a new order, if desired.

Reference Values: Not applicable


Candida auris, Molecular Detection, PCR, Blood

Clinical Information: Candida auris is a yeast that was first identified as causing disease in an individual in Japan in 2009. Since then, cases have been reported in more than 30 countries worldwide. The first case of Candida auris in the US was reported in 2015, and cases have been reported in a
number of states. In addition to causing disease, Candida auris can colonize individuals without signs or symptoms of disease. Candida auris can cause serious and sometimes fatal infections, is often resistant to one or more classes of antifungal drugs, and inappropriate treatment may occur as it can be misidentified in the laboratory. In addition, Candida auris appears to be more resistant to disinfection than other yeasts, leading to prolonged survival in the environment and increasing the possibility of transmission in hospitals and nursing homes. In December 2018, the Center for Disease Control and Prevention (CDC) recommended that health care facilities implement routine surveillance screening of patients who have had an overnight stay in a health care facility outside of the US over the past year, particularly if the hospitalization was in a country with confirmed cases of Candida auris. The CDC also recommended considering screening of patients who have been hospitalized outside of the US and have a documented infection or colonization with a carbapenamase-producing Gram-negative bacteria. These patients have frequently been found to have Candida auris colonization as well. A second group of people for whom screening is recommended includes health care workers who have been in close contact with patients who have previously unrecognized Candida auris infection or colonization. The Candida auris polymerase chain reaction (PCR) assay detects and identifies Candida auris from blood or urine specimens and also from swabs including combination groin/axilla surveillance swabs and nares surveillance swabs.

**Useful For:** Detection of Candida auris in whole blood specimens. This test should not be used to determine cure or to monitor response to therapy.

**Interpretation:** A positive result indicates the presence of Candida auris DNA. A negative result indicates the absence of detectable Candida auris DNA. An inhibited result indicates that inhibitors are present in the specimen that could prevent the detection of Candida auris DNA. A new specimen can be resubmitted under a new order, if desired.

**Reference Values:**
Not applicable

**Clinical References:**

**CAURP 607878**

**Candida auris, Molecular Detection, PCR, Random, Urine**

**Clinical Information:** Candida auris is a yeast that was first identified as causing disease in an individual in Japan in 2009. Since then, cases have been reported in more than 30 countries worldwide. The first case of Candida auris in the US was reported in 2015, and cases have been reported in a number of states. In addition to causing disease, Candida auris can colonize individuals without signs or symptoms of disease. Candida auris can cause serious and sometimes fatal infections, is often resistant to one or more classes of antifungal drugs, and inappropriate treatment may occur as it can be misidentified in the laboratory. In addition, Candida auris appears to be more resistant to disinfection than other yeasts, leading to prolonged survival in the environment and increasing the possibility of transmission in hospitals and nursing homes. In December 2018, the Center for Disease Control and Prevention (CDC) recommended that health care facilities implement routine surveillance screening of patients who have had an overnight stay in a health care facility outside of the US over the past year, particularly if the hospitalization was in a country with confirmed cases of Candida auris. The CDC also recommended considering screening of patients who have been hospitalized outside of the US and have a documented infection or colonization with a carbapenamase-producing Gram-negative bacteria. These patients have frequently been found to have Candida auris colonization as well. A second group of people for whom screening is recommended includes health care workers who have been in close contact with patients who have previously unrecognized Candida auris infection or colonization. The Candida auris polymerase chain reaction (PCR) assay detects and identifies Candida auris from blood or urine specimens and also from swabs including combination groin/axilla surveillance swabs and nares surveillance swabs.
**Useful For:** Detection of Candida auris in urine specimens This test should not be used to determine cure or to monitor response to therapy.

**Interpretation:** A positive result indicates the presence of Candida auris DNA. A negative result indicates the absence of detectable Candida auris DNA. An inhibited result indicates that inhibitors are present in the specimen that could prevent the detection of Candida auris DNA. A new specimen can be resubmitted under a new order, if desired.

**Reference Values:**
Not applicable

**Clinical References:**

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**Cannabidiol, Serum**

**Clinical Information:** Mean peak CBD plasma concentrations at 3-4 hours post-dose with Sativex at a low dose (5.4 mg of Delta-9 THC and 5.0 mg of Cannabidiol) were 1.6 +/- 0.4 ng/mL and at a high dose (16 mg of Delta-9 THC and 15 mg of Cannabidiol) were 6.7 +/- 2.0 ng/mL. Following high dose 400 and 800 mg oral synthetic CBD in corn oil administration, mean peak CBD plasma concentrations occurred within 1.5-3 hours post-dose and were 181.2 +/- 39.8 and 221.1 +/- 35.6 ng/mL, respectively. The ratio of blood to serum or plasma concentration is unknown for this analyte.

**Reference Values:**
Reporting limit determined each analysis
Units: ng/mL

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**Cannabinoid Analysis, Whole Blood**

**Reference Values:**
Cannabinoid Screen:
THC (MARIJUANA) Metabolite- Negative; Cutoff: 5 ng/mL
Cannabinoid Confirmation:
Tetrahydrocannabinol (THC)
Carboxy-THC
Hydroxy-THC
Cannabinol
Cannabidiol
Confirmation threshold: 1.0 ng/mL

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**Caraway, IgE, Serum**

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

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

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

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**CARBAMAZEPINE HYPERSONSITIVITY PHARMACOGENOMICS, VARIES**

**Clinical Information:** Carbamazepine and oxcarbazepine are aromatic anticonvulsants, as are eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital. Carbamazepine is FDA-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Oxcarbazepine is FDA-approved for the treatment of partial seizures. A minority of carbamazepine- or oxcarbazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. Drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) may also be related to carbamazepine exposure. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. According to the FDA label for oxcarbazepine, the rate of TEN and SJS among individuals exposed to oxcarbazepine exceeds the background incidence by a factor of 3- to 10-fold, but this is expected to be an underestimate due to underreporting. Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the HLA-B*15:02 allele varies throughout Asia: 10% to 15% frequency in Chinese; 2% to 4% frequency in Southeast Asians.
and Indians; and less than 1% frequency in Japanese and Koreans. This allele is strongly associated with greater risk of SJS and TEN in patients treated with carbamazepine or oxcarbazepine and has also been associated with SJS/TEN with phenytoin use. There is very limited evidence associating SJS/TEN/DRESS or MPE and other aromatic anticonvulsants in patients who are positive for HLA-B*15:02. The HLA-A*31:01 allele, which has a prevalence of 2% to 5% in Northern European populations, 6% among Hispanic/South American populations, and 8% among Japanese populations, has been significantly associated with greater risk of MPE, DRESS, and SJS/TEN among patients treated with carbamazepine. In the absence of HLA-A*31:01, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The evidence linking other aromatic anticonvulsants with SJS/TEN in the presence of the HLA-A*31:01 allele is weaker; however, an alternative medication should be chosen with caution. The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the HLA-B*15:02 allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of HLA-A*31:01 allele with drug-associated cutaneous adverse reactions regardless of ethnicity, but it does not specifically mandate screening of patients. The FDA-approved label for oxcarbazepine indicates that testing for the presence of the HLA-B*15:02 allele should be considered in patients with ancestry including genetically at-risk populations prior to initiation of therapy. According to the most recent Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, patients who are HLA-B*15:02 positive should not be prescribed carbamazepine or oxcarbazepine if alternative agents are available; however, caution should be used in selecting an alternative medication as there is weaker evidence that also links other aromatic anticonvulsants with SJS/TEN in patients positive for HLA-B*15:02. Furthermore, phenytoin is the subject of a separate CPIC guideline with recommendations to avoid phenytoin in HLA-B*15:02 positive individuals, along with additional recommendations based on CYP2C9 genotype. Patients who are HLA-A*31:01 positive should not be prescribed carbamazepine if alternative agents are available. However, although very limited evidence links SJS/TEN/DRESS/MPE with other aromatic anticonvulsants, among HLA-A*31:01-positive patients, caution should be used in selecting an alternative medication.

**Useful For:** Identifying individuals with increased risk of risk of carbamazepine- or oxcarbazepine-associated cutaneous adverse reactions

**Interpretation:** The presence of the HLA-B*15:02 and/or HLA-A*31:01 allele confers increased risk for hypersensitivity to carbamazepine. The presence of the HLA-B*15:02 allele also confers increased risk for hypersensitivity to oxcarbazepine and phenytoin. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
carbamazepine-10,11-epoxide (CBZ10-11), which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: -Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) -Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine -High-dose carbamazepine therapy, especially in combination with the above conditions

Useful For: Monitoring patients exhibiting symptoms of carbamazepine toxicity whose total serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide Free carbamazepine concentration may also be useful to monitor in patients with altered or unpredictable protein binding capacity

Interpretation: The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually less than or equal to 0.2 mcg/mL in symptomatic adults and less than or equal to 0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

Reference Values:
CARBAMAZEPINE, TOTAL
  Therapeutic: 4.0-12.0 mcg/mL
  Critical value: > or =15.0 mcg/mL

CARBAMAZEPINE-10,11-EPOXIDE
  Therapeutic: 0.4-4.0 mcg/mL
  Toxic concentration: > or =8.0 mcg/mL

CARBAMAZEPINE, FREE
  Therapeutic: 1.0-3.0 mcg/mL
  Critical value: > or =4.0 mcg/mL


Carbamazepine, Free and Total, Serum

Clinical Information: Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures. It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid. Under normal circumstances, the carbamazepine that circulates in blood is 75% protein bound. In severe uremia, carbamazepine may be displaced from protein, resulting in a higher free (unbound) fraction of the drug circulating in blood. Since neurologic activity and toxicity are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine level may be useful in patients with severe uremia.

Useful For: Monitoring carbamazepine (free and total) therapy in uremic patients
**Interpretation:** In patients with normal renal function, optimal response is often associated with free (unbound) carbamazepine levels greater than 1.0 mcg/mL, and toxicity may occur when the free carbamazepine is greater than or equal to 4.0 mcg/mL. In uremic patients, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free levels. Toxicity may occur in these patients when the free carbamazepine level is greater than or equal to 4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. They are best used as a guide in dose adjustment.

**Reference Values:**

- **CARBAMAZEPINE, TOTAL**
  - Therapeutic: 4.0-12.0 mcg/mL
  - Critical value: > or =15.0 mcg/mL

- **CARBAMAZEPINE, FREE**
  - Therapeutic: 1.0-3.0 mcg/mL
  - Critical value: > or =4.0 mcg/mL

**Clinical References:**

uremia, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free carbamazepine levels. Toxicity may occur when the free carbamazepine level is greater than or equal to 4.0 mcg/mL (even though the total carbamazepine concentration is < 15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. Serum levels are best used as a guide in dose adjustment.

**Reference Values:**
- Therapeutic concentration: 1.0-3.0 mcg/mL
- Critical value: > or = 4.0 mcg/mL

**Clinical References:**
1. Svinarov DA, Pippenger CE: Relationships between carbamazepine-diol, carbamazepine-epoxide, and carbamazepine total and free steady-state concentrations in epileptic patients: the influence of age, sex, and comedication. Ther Drug Monit 1996;18:660-665

**CARTA 37035 Carbamazepine, Total, Serum**

**Clinical Information:** Carbamazepine (Tegretol) is used in the control of partial seizures with both temporal lobe and psychomotor symptoms, and for generalized tonic-clonic seizures. It is also used for analgesia in trigeminal neuralgia. Carbamazepine exhibits a volume of distribution of 1.4 L/kg with an elimination half-life of 15 hours. Protein binding averages 70%. Carbamazepine-10,11-epoxide (CBZ10-11) is an active metabolite that represents the predominant form of the drug in children. The volume of distribution of CBZ10-11 is 1.1 L/kg, and the half-life is 5-8 hours. Aplastic anemia and agranulocytosis are rare side effects of treatment with carbamazepine; baseline hematologic data should be documented before treatment is initiated. Toxicity associated with carbamazepine overdose occurs when the blood level is 15.0 mcg/mL or higher and is typified by irregular breathing, muscle irritability, and hyperreflexia; followed by hyporeflexia, tachycardia, hypotension, and impaired consciousness with coma in severe toxicity. The higher the blood level, the more severe the symptoms.

**Useful For:** Monitoring therapy, Determining compliance, Assessing toxicity

**Interpretation:** Dosage adjustments are usually guided by monitoring blood levels. Most patients respond well when the serum concentration is in the range of 4.0 to 12.0 mcg/mL. Toxicity often occurs when levels are greater than or equal to 15.0 mcg/mL.

**Reference Values:**
- Therapeutic: 4.0-12.0 mcg/mL
- Critical value: > or = 15.0 mcg/mL

**Clinical References:**

**CARBG 37036 Carbamazepine-10,11-Epoxide, Serum**

**Clinical Information:** Carbamazepine is a common antiepileptic drug. It is a first-line drug for
Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11) which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: -Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) -Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine -High-dose carbamazepine therapy, especially in combination with the above conditions

**Useful For:** Monitoring patients exhibiting symptoms of carbamazepine toxicity whose total serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide, which can accumulate to concentrations equivalent to carbamazepine

**Interpretation:** The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually < or =0.2 mcg/mL in symptomatic adults and < or =0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

**Reference Values:**
- **CARBAMAZEPINE, TOTAL**
  - Therapeutic: 4.0-12.0 mcg/mL
  - Critical value: > or =15.0 mcg/mL
- **CARBAMAZEPINE-10,11-EPOXIDE**
  - Therapeutic concentration: 0.4-4.0 mcg/mL
  - Toxic concentration: > or =8.0 mcg/mL

**Clinical References:**

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**CARNB**

**Carbapenemase Detection-Carba NP Test (Bill Only)**

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

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**CARNP**

**Carbapenemase Detection-Carba NP Test, Varies**

**Clinical Information:** Gram-negative bacilli (GNB) with acquired carbapenemases have disseminated worldwide, rendering them a global threat. The therapeutic armamentarium for infections caused by carbapenem-resistant Enterobacteriaceae (CRE) is limited, and CRE infections have been associated with significant mortality. Enterobacteriaceae harboring Klebsiella pneumoniae carbapenemase are endemic in some regions of the United States, and although still sporadic, GNB harboring New Delhi metallo-beta-lactamase have been reported from several states. Timely detection of these carbapenemases (along with emerging carbapenemases such as OXA-48 and VIM) is
important. Detection is challenging since isolates may have only borderline reductions in susceptibility to carbapenems, and carbapenem resistance may be mediated by mechanisms other than carbapenemases (eg, AmpC or extended-spectrum beta-lactamase with decreased membrane permeability). While molecular methods are confirmatory, testing may not be immediately available and may be limited by the number of targets assayed. The modified Hodge test suffers from lack of specificity, a long turnaround time, and poor sensitivity for metallo-beta-lactamase detection. The Carba NP test is preferred over the modified Hodge test due to improved specificity and faster turnaround time. The Carba NP test is more specific than and as sensitive as the carbapenemase-modified Hodge test. If an isolate is suspected to possess KPC or NDM carbapenemase (eg, due to local epidemiology), KPC and NDM PCR (KPNRP / KPC (blaKPC) and NDM (blaNDM) in Gram-Negative Bacilli, Molecular Detection, PCR) may be preferred over the Carba NP test.

**Useful For:** Confirmation of carbapenemase production from pure isolates of Enterobacteriaceae or Pseudomonas aeruginosa

**Interpretation:** A positive result indicates production of a carbapenemase by the isolate submitted for testing. A negative result indicates lack of production of a carbapenemase by the isolate submitted for testing.

**Reference Values:**

Negative

**Clinical References:**


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**Carbohydrate Antigen 19-9 (CA 19-9), Pancreatic Cyst Fluid**

**Clinical Information:** Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen, which has been used as a tumor marker. Serum CA 19-9 concentrations may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, colon cancer, or pancreatic cancer. While serum CA 19-9 is neither sensitive nor specific for pancreatic cancer, concentrations of CA 19-9 in pancreatic cyst fluid may help determine whether a pancreatic cyst is benign. Cystic lesions of the pancreas are of various types: -Benign cysts: Å -Inflammatory cysts (pseudocysts) Å -Serous cysts (serous cystadenoma) -Mucinous cysts: Å -Premalignant (mucinous cystadenoma) Å -Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia) Pancreatic cyst fluid CA 19-9 results should be used in conjunction with imaging studies, cytology, and other cyst-fluid tumor markers, such as carcinoembryonic antigen and amylase.

**Useful For:** As an adjunct in the assessment of pancreatic cysts, when used in conjunction with carcinoembryonic antigen, amylase, imaging studies and cytology

**Interpretation:** Cyst fluid carbohydrate antigen 19-9 (CA19-9) concentrations less than or equal to 37 U/mL indicate a low risk for a mucinous cyst and are more consistent with serous cystadenoma or pseudocyst. The sensitivity and specificity are approximately 19% and 98%, respectively, at this concentration. Correlation of these test results with cytology and imaging is recommended.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

**Carbohydrate Antigen 19-9 (CA 19-9), Peritoneal Fluid**

**Clinical Information:** Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylos ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in the serum patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Measurement of CA 19-9 in ascitic fluid is sometimes used in combination with cytology for detecting malignancy-related ascites.

**Useful For:** An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

**Interpretation:** A peritoneal fluid carbohydrate antigen 19-9 (CA 19-9) concentration >32 U/mL is suspicious, but not diagnostic, of a malignancy-related ascites. This clinical decision limit cutoff yielded 44% sensitivity and 93% specificity in a study of 137 patients presenting with ascites. However, ascites caused by malignancies not associated with increase serum CA 19-9 concentrations, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations <32 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CA 19-9 levels in serum.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Carbohydrate Antigen 19-9 (CA 19-9), Pleural Fluid**

**Clinical Information:** Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, requiring cytological examination of the fluid. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology findings. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. Healthy adults typically produce low to undetectable levels of CA 19-9. Serum concentrations of CA 19-9 may be elevated in patients with certain malignancies that secrete CA 19-9 into circulation, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. Pleural fluid concentrations of CA 19-9 have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CA 19-9 and elevate serum CA 19-9 concentrations, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers, typically also elevate CA 19-9 in pleural fluid. In contrast, malignancies that do not secrete CA 19-9, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CA 19-9 in pleural fluid comparable to concentrations observed in nonmalignant effusions. CA 19-9 results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.
Useful For: An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

Interpretation: A pleural fluid carbohydrate antigen 19-9 (CA 19-9) concentration of 20.0 U/mL or higher is suspicious, but not diagnostic, of a malignant source of the effusion. This cutoff yielded a sensitivity of 35%, specificity of 95%, and positive predictive value of 88% in a study of 200 patients presenting with effusion. CA 19-9 concentrations were significantly higher in effusions caused by CA 19-9-secreting malignancies, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. However, effusions caused by non-CA 19-9-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations below 20.0 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CA 19-9-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

Reference Values: An interpretive report will be provided.


Carbohydrate Antigen 19-9 (CA 19-9), Serum

Clinical Information: Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Benign conditions such as cirrhosis, cholestasis, and pancreatitis also result in elevated serum CA 19-9 concentrations but in these cases values usually are below 1000 U/mL. Individuals that are Lewis negative (5%-7% of the population) do not express CA 19-9 due to the lack of the enzyme fucosyltransferase needed for CA 19-9 production. In these individuals, a low or undetectable serum CA 19-9 concentration is not informative regarding cancer recurrence.

Useful For: As a potential adjunct for diagnosis and monitoring of pancreatic cancer Potentially differentiating patients with cholangiocarcinoma and primary sclerosing cholangitis (PSC) from those with PSC alone

Interpretation: Serial monitoring of carbohydrate antigen 19-9 (CA 19-9) should begin prior to therapy to verify post-therapy decreases in CA 19-9 and to establish a baseline for evaluating possible recurrence. Single values of CA 19-9 are less informative. Elevated values may be caused by a variety of malignant and nonmalignant conditions including cholangiocarcinoma, pancreatic cancer, and colon cancer.

Reference Values: <35 U/mL


Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum

Clinical Information: Glycosylation is the post-translational modification of proteins and lipids by the addition of glycans (sugars and sugar chains) in a complex stepwise fashion in the endoplasmic reticulum, Golgi apparatus, cytosol and sarcosomal membrane. Congenital disorders of glycosylation (CDG), are a group of over 150 inherited metabolic disorders characterized by abnormal protein and lipid
glycosylation. There are 2 main groups of CDG: type I, characterized by defects in the assembly or transfer of the dolichol-linked glycan in either the cytosol or endoplasmic reticulum (ER) and type II, involving processing defects of the glycan in the ER and Golgi apparatus. In addition, there are 2 categories of glycosylation: N-glycosylation where N-linked glycans are attached to a protein backbone via an asparagine residue on the protein, and O-glycosylation where O-glycans are attached to the hydroxyl group of threonine or serine. Apolipoprotein CIII (Apo-CIII) isoforms, with a single core 1 mucin type O-glycosylate protein, is a complementary evaluation for the CDG type II profile. This analysis will evaluate mucin type O-glycosylation, a defect involving the Golgi apparatus, which is detected biochemically by the change in ratios of the 3 isoforms. CDG typically present as multi-systemic disorders with a broad clinical spectrum including, but not limited to, developmental delay, hypotonia, with or without neurological abnormalities, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases ranging from a mild presentation in adults and children to severe multi-organ dysfunctions causing infantile lethality. In some subtypes, phosphomannose isomerase-CDG (MPI-CDG or CDG-IIb) in particular, intelligence is not compromised. CDG should be suspected in all patients with neurological abnormalities including developmental delay and seizures, brain abnormalities such as cerebellar atrophy or hypoplasia as well as unexplained liver dysfunction. Abnormal subcutaneous fat distribution and chronic diarrhea each may or may not be present. The differential diagnosis of abnormal transferrin patterns also includes liver disease not related to CDG including galactosemia, hereditary fructose intolerance in acute crisis, and liver disease of unexplained etiology. Transferrin and apolipoprotein CIII isoform analysis are the initial screening tests for CDG. The results of the transferrin and apolipoprotein CIII isoform analysis should be correlated with the clinical presentation to determine the most appropriate follow-up testing strategy including enzyme, molecular, and research-based testing. Enzymatic analysis for phosphomannomutase and phosphomannose isomerase in leukocytes (PMMIL / Phosphomannomutase and Phosphomannose Isomerase, Leukocytes) should be performed if either PMM2-CDG (CDG-Ia) or MPI-CDG (CDG-IIb) is suspected. Other glycosylation pathways, in addition to N- and O-glycosylation, have been elucidated, in particular, glycoprophosphatidylinositol (GPI)-anchored protein glycosylation disorders in which there is absent or decreased expression of all the GPI-linked antigens, and alpha-dystroglycanopathies caused by impaired synthesis of O-mannose glycans. Neither class of disorders are routinely picked up by CDG analysis in serum but are typically diagnosed using molecular methods (CDGGP / Congenital Disorders of Glycosylation Gene Panel, Varies).

**Useful For:** Screening for congenital disorders of glycosylation

**Interpretation:** Positive test results could be due to a genetic or nongenetic condition; additional confirmatory testing is required. In serum, the bi-antennary transferrin (di-oligo) fraction is the most abundant transferrin isoform. Congenital disorders of glycosylation (CDG)-I generally shows increases in mono-oligo- and/or a-oligo transferrin isoforms whereas CDG-II shows elevated increased transferrin with truncated glycans of varying degree depending on the type of defect.(1) Results are reported as the mono-oligosaccharide/di-oligosaccharide transferrin ratio, the a-oligosaccharide/di-oligosaccharide transferrin ratio, the tri-sialo/di-oligosaccharide transferrin ratio, and the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio, and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio. The report will include the quantitative results and an interpretation. The congenital disorders of glycosylation (CDG) profiles are can be categorized into 5 types: 1. CDG type I profile. Mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio are abnormal. This group should have the apolipoprotein C-III profile within the normal ranges, because the Golgi system is not affected in CDG type I. 2. CDG type II profile. The tri-sialo/di-oligosaccharide transferrin ratio is abnormal. In this category, the apolipoprotein C-III profile will have 2 scenarios: A. The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio will be abnormal. In this case, the defect is most likely glycan processing in the Golgi apparatus; therefore, a CDG (conserved oligomeric Golgi [COG]) defect or defect that alters the Golgi apparatus is likely. B. The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio are normal. In this case, most likely the defects do not involve the Golgi system, thus the molecular defect is different. 3. CDG mixed type profile (type I and II together). In this type of profile one can have abnormal tri-sialo/di-oligosaccharide transferrin ratio with the mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio abnormal, and may have the apolipoprotein
CIII-1/apolipoprotein CIII-2 ratio and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio normal or abnormal, depending if the defects involve Golgi apparatus. 4. CDG with normal transferrin and apolipoprotein profile. Some CDG (eg, PGM3, some ALG13, MOGS, NGLY1, SLC35C1, Fut8) pose a problem for their detection. Thus, a careful medical history, physical exam, and analysis of other protein status may be informative for general protein glycosylation defects. If suspicious for either NGLY1- or MOGS-CDG, specific oligosaccharides in urine can be detected (OLIGU / Oligosaccharide Screen, Random, Urine). 5. When the profile cannot be categorized following the above classification, the abnormalities will be reported descriptively according to the molecular mass of the glycan isoform structures. Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to more precisely identify the correct form of CDG. If applicable, treatment options, the name and telephone number of contacts who may provide studies at Mayo Clinic or elsewhere, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided. See Transferrin and Lipoprotein-CIII Isoform Analysis in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Normal</th>
<th>Indeterminate</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin mono-oligo/di-oligo ratio</td>
<td>&lt; or =0.06</td>
<td>0.07-0.09</td>
<td>&gt; or =0.10</td>
</tr>
<tr>
<td>Transferrin A-oligo/di-oligo ratio</td>
<td>&lt; or =0.011</td>
<td>0.012-0.021</td>
<td>&gt; or =0.022</td>
</tr>
<tr>
<td>Transferrin tri-sialo/di-oligo ratio</td>
<td>&lt; or =0.05</td>
<td>0.06-0.12</td>
<td>&gt; or =0.13</td>
</tr>
<tr>
<td>Apo CIII-1/Apo CIII-2 ratio</td>
<td>&lt; or =2.91</td>
<td>2.92-3.68</td>
<td>&gt; or =3.69</td>
</tr>
<tr>
<td>Apo CIII-0/Apo CIII-2 ratio</td>
<td>&lt; or =0.48</td>
<td>0.49-0.68</td>
<td>&gt; or =0.69</td>
</tr>
</tbody>
</table>

**Clinical References:**


**Carbohydrate Deficient Transferrin, Adult, Serum**

**Clinical Information:** Chronic alcoholism causes a transient change in the glycosylation pattern of transferrin where the relative amounts of disialo- and asialotransferrin (carbohydrate deficient transferrin: CDT) are increased over the amount of normally glycosylated tetrasialotransferrin. This recognition led to the use of CDT in serum as a marker for chronic alcohol abuse. CDT typically normalizes within several weeks of abstinence of alcohol use. However, it is important to recognize that there are other causes of abnormal CDT levels, which include congenital disorders of glycosylation and other genetic and nongenetic causes of acute or chronic liver disease. CDT testing alone is not recommended for general screening for alcoholism; however, when combined with other methods (ie, gamma-glutamyltransferase,
mean corpuscular volume, patient self-reporting, ethylglucuronide analysis), clinicians can expect to identify the majority of patients who consume a large amount of alcohol.

**Useful For:** An indicator of chronic alcohol abuse This test is not appropriate for screening patients for congenital disorders of glycosylation.

**Interpretation:** Patients with chronic alcoholism may develop abnormally glycosylated transferrin isoforms (ie, carbohydrate deficient transferring: CDT >0.12). CDT results from 0.11 to 0.12 are considered indeterminate. Patients with liver disease due to genetic or nongenetic causes may also have abnormal results.

**Reference Values:**
- < or =0.10
- 0.11-0.12 (indeterminate)

**Clinical References:**

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**Carbohydrate, Urine**

**Clinical Information:** Carbohydrates are a group of mono-, di-, and oligosaccharides of endogenous and exogenous sources. Their presence frequently reflects dietary consumption but can indicate specific pathology if either a particular saccharide or a particular excretory pattern is present. Most saccharides (except glucose) have low renal thresholds and are readily excreted in the urine. In addition to several other saccharide species, chromatography of urinary saccharides identifies galactose and fructose and is, therefore, useful to screen for inborn errors of galactose and fructose metabolism. Xylose may also be detected in individuals with hereditary pentosuria, a benign trait with high frequency among individuals with Ashkenazi Jewish descent.

**Useful For:** Screening for conditions associated with increased excretion of fructose, galactose, and xylose This test is not recommended as a follow up test for abnormal newborn screening for galactosemia.

**Interpretation:** An interpretive comment is provided that includes the name of the identified saccharide and the probable source.

**Reference Values:**
- Negative
- If positive, carbohydrate is identified.

**Clinical References:**
Carbon Monoxide, Blood

Clinical Information: Carbon monoxide (CO) is a colorless, odorless, tasteless gas that is a product of incomplete combustion of carbonaceous material. CO poisoning causes hypoxia because CO binds to hemoglobin with an affinity 250 times greater than that of oxygen, thus preventing delivery of oxygen to the tissues, but concentrations greater than 20% are associated with symptoms of toxicity (e.g., headache, fatigue, dizziness, confusion, nausea, vomiting, increased pulse and respiratory rate). CO levels greater than 50% are potentially fatal. Common exogenous sources of carbon monoxide include cigarette smoke, gasoline engines, and improperly ventilated home heating units. Small amounts of carbon monoxide are produced endogenously in the metabolic conversion of heme to biliverdin. This endogenous production of carbon monoxide is accelerated in hemolytic anemias.

Useful For: Verifying carbon monoxide toxicity in cases of suspected exposure

Interpretation: The toxic effects of carbon monoxide can be seen in levels above 20% carboxyhemoglobin. It must be emphasized that the carboxyhemoglobin concentration, although helpful in diagnosis, does not always correlate with the clinical findings or prognosis. Factors other than carboxyhemoglobin concentration that contribute to toxicity include length of exposure, metabolic activity, and underlying disease, especially cardiac or cerebrovascular disease. Moreover, low carboxyhemoglobin concentrations relative to the severity of poisoning may be observed if the patient was removed from the carbon monoxide-contaminated environment a significant amount of time before blood sampling. An insidious effect of carbon monoxide poisoning is the delayed development of neuropsychiatric sequelae, which may include personality changes, motor disturbances, and memory impairment. These manifestations do not correlate with the length of exposure or with the maximum blood carboxyhemoglobin concentration.

Reference Values:
Normal Concentration
Non-Smokers: 0-2%
Smokers: < or =9%
Toxic concentration: > or =20%


Carbonic Anhydrase IX (CA-IX) Immunostain, Technical Component Only

Clinical Information: Carbonic anhydrase IX (CA-IX) is a hypoxia-induced protein expressed in the gastrointestinal tract, mainly in the stomach. Expression of CA-IX is useful in the diagnosis of clear cell renal cell carcinoma and clear cell papillary renal cell carcinoma. It can assist in distinguishing clear cell carcinoma from chromophobe carcinoma, oncocytoma, and several other renal cell carcinomas.

Useful For: Diagnosis of clear cell renal cell carcinoma and clear cell papillary renal cell carcinoma

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**Carboxy-Tetrahydrocannabinol (THC) Confirmation, Chain of Custody, Random, Urine**

**Clinical Information:** Delta-9-tetrahydrocannabinol is the active agent of the popularly abused street drug, marijuana. After consumption, either by inhalation or ingestion, the drug is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid. The immunoassay used to screen for tetrahydrocannabinol (THC) is designed to cross-react with THC carboxylic acid. In almost all medico-legal cases and in screening of employees, or when the patient adamantly denies THC use and the immunoassay test is positive, confirmation of the result by gas chromatography-mass spectrometry is required. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. This includes a record of the disposition of a specimen to document the personnel who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana) in urine specimens handled through the chain-of-custody process.

**Interpretation:** The presence of tetrahydrocannabinol carboxylic acid (THC-COOH), a major metabolite of delta-9-tetrahydrocannabinol (THC), in urine at concentrations greater than 15 ng/mL is a strong indicator that the patient has used marijuana. THC-COOH has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine greater than 100 ng/mL indicates relatively recent use, probably within the past 7 days. Levels greater than 500 ng/mL suggest chronic and recent use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

**Reference Values:**
- **Negative**
  - Positives are reported with a quantitative GC-MS result.

  - **Cutoff concentrations:**
    - **IMMUNOASSAY SCREEN**
      - <50 ng/mL
    - **THC CARBOXYLIC ACID BY GC-MS**
      - <3 ng/mL

**Clinical References:**
Clinical Information: Delta-9-tetrahydrocannabinol (THC) is the active agent of the popularly abused street drug, marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid. In almost all medico-legal cases and in screening of employees, or when the patient adamantly denies THC use and the immunoassay test is positive, confirmation of the result by gas chromatography-mass spectrometry (GC-MS) is required.

Useful For: Confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana)

Interpretation: The presence of tetrahydrocannabinol carboxylic acid (THC-COOH), a major metabolite of delta-9-tetrahydrocannabinol, in urine at concentrations greater than 15.0 ng/mL is a strong indicator that the patient has used marijuana. The metabolite of marijuana (THC-COOH) has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine greater than 100.0 ng/mL indicates relatively recent use, probably within the past 7 days. Levels greater than 500.0 ng/mL suggest chronic and recent use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

Reference Values:
Negative

Cutoff concentration:
Carboxy-THC- by GC/MS <3.0 ng/mL


Carcinoembryonic Antigen (CEA), Pancreatic Cyst Fluid

Clinical Information: Cystic lesions of the pancreas are of various types including: -Benign cysts: Â·Inflammatory cysts (pseudocysts) Â·Serous cysts (serous cystadenoma) -Mucinous cysts: Â·Premalignant (mucinous cystadenoma) Â·Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia) The diagnosis of pancreatic cyst type is often difficult and may require correlating imaging studies with results of cytological examination and tumor marker testing performed on cyst aspirates. Various tumor markers have been evaluated to distinguish non-mucinous, nonmalignant pancreatic cysts from mucinous cysts, which have a high likelihood of malignancy. Carcinoembryonic antigen (CEA) has been found to be the most reliable tumor marker for identifying those pancreatic cysts that are likely mucinous. In cyst aspirates, CEA concentrations of 200 ng/mL and above are highly suspicious for mucinous cysts. The greater the CEA concentration, the greater the likelihood that the mucinous cyst is malignant. However, CEA testing does not reliably distinguish between benign, premalignant, or malignant mucinous cysts. CEA test results should be correlated with the results of imaging studies, cytology, other cyst fluid tumor markers (ie, amylase and CA 19-9), and clinical findings for diagnosis.

Useful For: When used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers: -Distinguishing between mucinous and nonmucinous pancreatic cysts -Determining the likely type of malignant pancreatic cyst

Interpretation: A pancreatic cyst fluid carcinoembryonic antigen (CEA) concentration of 200 ng/mL and higher is very suggestive for a mucinous cyst but is not diagnostic. The sensitivity and specificity for mucinous lesions are approximately 62% and 93%, respectively, at this concentration. Cyst fluid CEA concentrations of 5 ng/mL and below indicate a low risk for a mucinous cyst, and are more consistent with serous cystadenoma, fluid collections complicating pancreatitis, cystic neuroendocrine tumor, or metastatic lesions. CEA values between these extremes have limited diagnostic value.

Reference Values:
An interpretive report will be provided.
Carcinoembryonic Antigen (CEA), Peritoneal Fluid

Clinical Information:
Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carcinoembryonic antigen (CEA) is a glycoprotein that is shed from the surface of malignant cells. Measurement of CEA in ascitic fluid has been proposed as a helpful test in detecting malignancy-related ascites given the limited sensitivity of cytology.

Useful For:
An adjunct to cytology to differentiate between malignancy-related and benign causes of ascites formation

Interpretation:
A peritoneal fluid carcinoembryonic antigen (CEA) concentration >6.0 ng/mL is suspicious but not diagnostic of malignancy-related ascites. This clinical decision limit cutoff yielded 48% sensitivity and 99% specificity in a study of 137 patients presenting with ascites. CEA concentrations were significantly higher in ascites caused by malignancies known to be associated with elevated serum CEA levels including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, ascites caused by other malignancies such as lymphoma, mesothelioma, leukemia, and melanoma and hepatocellular carcinoma, routinely had CEA concentrations <6.0 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CEA levels in serum.

Reference Values:
An interpretive report will be provided.

Clinical References:

Carcinoembryonic Antigen (CEA), Pleural Fluid

Clinical Information:
Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, often requiring cytological examination of the pleural fluid and imaging studies of the pleural tissue. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology and imaging findings. Carcinoembryonic antigen (CEA) is a glycoprotein produced during fetal development. Nonsmoking, healthy adults typically produce low to undetectable levels of CEA. Serum concentrations of CEA may be elevated in patients with certain malignancies that secrete CEA into
circulation, including medullary thyroid carcinoma and breast, gastrointestinal tract, colorectal, liver, lung, ovarian, pancreatic, and prostate cancers. Pleural fluid concentrations of CEA have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CEA and elevate serum CEA concentrations, including lung, breast, ovarian, gastrointestinal, and colorectal cancers, typically also elevate CEA in pleural fluid. In contrast, malignancies that do not secrete CEA, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CEA in pleural fluid comparable to concentrations observed in non-malignant effusions. Elevated CEA concentrations in pleural fluid have also been reported with certain nonmalignant conditions, including liver cirrhosis, pancreatitis, complicated parapneumonic effusions and empyemas, and rarely with tuberculosis. CEA results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

**Useful For:** An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

**Interpretation:** A pleural fluid carcinoembryonic antigen (CEA) concentration of 3.5 ng/mL or higher is suspicious but not diagnostic of a malignant source of the effusion. This cutoff yielded a sensitivity of 52%, specificity of 95%, and part per volume of 93% in a study of 200 patients presenting with effusion. CEA concentrations were significantly higher in effusions caused by CEA-secreting malignancies, including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, effusions caused by non-CEA-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CEA concentrations below 3.5 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CEA-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Serum markers are not specific for malignancy, and values may vary by method.

**Clinical References:**

### CEASF 90695

**Carcinoembryonic Antigen (CEA), Spinal Fluid**

**Clinical Information:** Carcinoembryonic antigen (CEA) normally is present in cerebrospinal fluid (CSF) in very low concentrations. Elevations in serum CEA can cause passive transfer to CSF. Tumors of the brain, especially metastatic tumors, can elevate CSF CEA.

**Useful For:** Detecting meningeal carcinomatosis and intradural or extradural infiltration

**Differentiating brain parenchymal metastasis from adenocarcinoma or squamous-cell carcinoma**

**Interpretation:** Increased values are seen in approximately 60% of patients with meningeal carcinomatosis.

**Reference Values:**
<0.6 ng/mL

Tumor markers are not specific for malignancy, and values may vary by method.

**Clinical References:**

### MCEA 70506

**Carcinoembryonic Antigen, Monoclonal Immunostain, Technical Component Only**

**Clinical Information:** In tissue sections of normal colon, carcinoembryonic antigen (CEA) is mainly localized at the apical border of the epithelial cells. Monoclonal CEA antibodies label the epithelium of colonic adenocarcinoma, normal adult colonic mucosa, and normal gastric foveolar mucus-producing cells.

**Useful For:** Marker of epithelial cells

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
3. Sumitoma S, Kumasa S, Mitani H, Mori M: Comparison of CEA distribution in lesions and tumors of salivary glands as determined with...
PCEAI 70535

Carcinoembryonic Antigen, polyclonal Immunostain, Technical Component Only

Clinical Information: Polyclonal carcinoembryonic antigen labels normal and neoplastic epithelium of the small and large intestine, stomach, and pancreatic ducts. The polyclonal antibody also reacts with biliary canaliculi and granulocytes.

Useful For: Marker of epithelial cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. A. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CARD 82491

Cardamom, IgE, Serum

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

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

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

Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**CVRMP 37002**

**Cardiovascular Risk Marker Panel, Serum**

**Clinical Information:** Cardiovascular disease is the number 1 cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually. Many of these events occur in individuals who have no prior symptoms. Standard risk factors, including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, predict only about 65% of individuals who will go on to have a cardiovascular event. Therefore, identification of patients with residual risk is important to target lifestyle and pharmaceutical intervention to those at higher risk of future events. Many additional risk markers have been identified for cardiovascular disease but few have emerged as independent risk markers. Two of these additional risk markers, high-sensitivity C-reactive protein (hsCRP) and lipoprotein (a) (Lp[a]), are clearly shown to be independently associated with increased risk of future cardiovascular events. Several recent guidelines have suggested that clinicians utilize hsCRP and Lp(a) in selected persons to augment risk classification, guide intensity of risk-reduction therapy and modulate clinical judgment when making therapeutic decision.(1-3) Prospective studies assessing these risk factors individually have determined them to be independently associated with increased risk for the development of ischemic events. Guidelines recommend measurement of additional risk markers in individuals who are at intermediate risk for developing cardiovascular disease, those with early atherosclerosis without explanation by abnormalities of traditional risk factors, and those with a strong family history of cardiovascular disease without the presence of traditional risk factors.

**Useful For:** Assessment for risk of developing cardiovascular disease, major adverse cardiovascular events, or ischemic cerebrovascular events

**Interpretation:** Specific interpretations are provided based on lipid results according to Mayo Clinic care process models. Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Clinic Laboratories reports (see Reference Values). More aggressive treatment strategies may be pursued in patients determined to be at increased risk. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>2-17 years</th>
<th>&gt;18 years</th>
</tr>
</thead>
</table>

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 499
Non-HDL Cholesterol (mg/dL) ** Acceptable: high: 120-144 High: > 145
or =145

LDL Cholesterol (mg/dL) ** Acceptable: high: 110-129 High: > 130
or =130

HDL Cholesterol (mg/dL) ** Low: low: 40-45 Acceptable: > 45
or =50

Total Cholesterol (mg/dL) ** Acceptable: high: 170-199 High: > 200
or =200

LIPOPROTEIN (a) (mg/dL) < or =30 mg/dL Values >30 mg/dL may suggest increased risk of coronary heart disease.

C-REACTIVE PROTEIN HIGH SENSITIVITY * Lower risk: Higher risk: >=2.0 mg/L Acute inflammation: >10.0 mg/L

Age 2-9 years 10-17 years >18 years

Triglycerides (mg/dL) ** Acceptable: high: 75-99 ** Acceptable: high: High: > or =100
or =100


FCRDE Carmine Dye/Red Dye Cochineal (Dactylopius coccus) IgE (Red # 4)

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 > or = 100 Very High Positive

Reference Values: <0.35 kU/L
Carnitine Palmitoyltransferase II Deficiency, Full Gene Analysis, Varies

Clinical Information: Carnitine palmitoyltransferase II (CPT II) deficiency is an autosomal recessive disorder of long-chain fatty-acid oxidation. There are 3 distinct clinical phenotypes: a lethal neonatal form, an early-onset infantile form, and a late-onset adult myopathic form. The lethal neonatal and early-onset infantile forms are characterized by liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia, peripheral myopathy and early death. The adult-onset myopathic form is the most common type and is characterized by exercise-induced muscle pain and weakness and may be associated with myoglobinuria. Males are more likely to be affected with the myopathic form than females. Initial screening can be done with plasma acylcarnitines. Definitive diagnosis can be made by detection of reduced CPT enzyme activity. Mutations in the CPT2 gene are responsible for CPT II deficiency and sequencing of this gene is recommended after positive biochemical analysis.

Useful For: Confirmation of diagnosis of carnitine palmitoyltransferase II deficiency. Carrier screening in cases where there is a family history of carnitine palmitoyltransferase II deficiency, but disease-causing mutations have not been identified in an affected individual.

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

Reference Values: An interpretive report will be provided.


Carnitine, Plasma

Clinical Information: Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Maintaining the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Collectively, their incidence is approximately 1 in 1000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions that could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

Useful For: Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency using plasma specimens.

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Carnitine (TC)</th>
<th>Free Carnitine (FC)</th>
<th>Acylcarnitine (AC)</th>
<th>AC/FC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =1 day</td>
<td>Range*</td>
<td>Range*</td>
<td>Range*</td>
<td>Range</td>
</tr>
<tr>
<td>2-7 days</td>
<td>17-41</td>
<td>10-21</td>
<td>3-24</td>
<td>0.2-1.4</td>
</tr>
<tr>
<td>8-31 days</td>
<td>19-59</td>
<td>12-46</td>
<td>4-15</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>32 days-12 months</td>
<td>38-68</td>
<td>27-49</td>
<td>7-19</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>13 months-6 years</td>
<td>35-84</td>
<td>24-63</td>
<td>4-28</td>
<td>0.1-0.8</td>
</tr>
<tr>
<td>7-10 years</td>
<td>28-83</td>
<td>22-66</td>
<td>3-32</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>11-17 years</td>
<td>34-77</td>
<td>22-65</td>
<td>4-29</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>34-78</td>
<td>25-54</td>
<td>5-30</td>
<td>0.1-0.8</td>
</tr>
</tbody>
</table>


**CARNU 81123**

**Carnitine, Random, Urine**

**Clinical Information:** Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally occurring short-chain acyl-CoA groups from the mitochondria -Maintaining the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions that could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias and fatty acid oxidation disorders Monitoring carnitine treatment

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

**Reference Values:**
FREE CARNITINE  
77-214 nmol/mg of creatinine

TOTAL CARNITINE  
180-412 nmol/mg of creatinine

RATIO  
Acylcarnitine to free carnitine: 0.7-3.4


**Carnitine, Serum**  
**Clinical Information:** Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Maintaining the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues  
Evaluation of carnitine in serum, plasma, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter disorders, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Collectively, their incidence is approximately 1 in 1000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions that could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency using serum specimens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total carnitine (TC)</th>
<th>Free carnitine (FC)</th>
<th>Acylcarnitine (AC)</th>
<th>AC/FC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range*</td>
<td>Range*</td>
<td>Range*</td>
<td>Range</td>
<td></td>
</tr>
</tbody>
</table>

CACTZ 35379

Carnitine-Acylcarnitine Translocase Deficiency, Full Gene Analysis, Varies

Clinical Information: Carnitine-acylcarnitine translocase (CACT) deficiency is a rare autosomal recessive disorder of fatty acid oxidation. The disease typically presents in the neonatal period with severe hypoketotic hypoglycemia, hyperammonemia, cardiac abnormalities, hepatic dysfunction, skeletal muscle weakness, encephalopathy, and early death. However, presentations at a later age with a milder phenotype have also been reported. Initial screening can be done with plasma acylcarnitines. Definitive diagnosis can be made by detection of reduced CACT enzyme activity. Mutations in the SLC25A20 gene are responsible for CACT deficiency, and sequencing of this gene is recommended after positive biochemical analysis.

Useful For: Confirmation of diagnosis of carnitine-acylcarnitine translocase (CACT) deficiency Carrier screening in cases where there is a family history of CACT deficiency, but disease-causing mutations have not been identified in an affected individual

Reference Values: An interpretive report will be provided.

**Carob, IgE, Serum**

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Carotene, Beta**

**Useful For:** Confirm the diagnosis of carotenoderma; detect fat malabsorption; depressed carotene levels may be found in cases of steatorrhea.

**Interpretation:** High levels are useful to rule out steatorrhea but lower values lack specificity. There is poor sensitivity. High in the serum of those ingesting large amounts of vegetables.

**Reference Values:**

3 - 91 ug/dL
Carrot IgG

Interpretation:

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

Carrot, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to carrot Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Casein IgG

Interpretation:

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

Casein, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to casein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.

**Cashew Component rAna o 3**

**Clinical Information:** This assay is used to detect allergen specific-IgE using the ImmunoCAP® FEIA method. In vitro allergy testing is the primary testing mode for allergy diagnosis.

**Interpretation:**
- Class IgE (kU/L) Comment
  - 0 <0.10 Negative
  - 0.10 - 0.34 Equivocal/Borderline
  - 0.35 - 0.69 Low Positive
  - 0.70 - 3.49 Moderate Positive
  - 3.50 - 17.49 High Positive
  - 17.50 - 49.99 Very High Positive
  - >49.99 Very High Positive

**Reference Values:**
- <0.10 kU/L

**Clinical References:**
- Rosenfeld L et al. Peanut Allergy in Peanut-Allergic Patients: Significance of Sequential Epitopes of Walnut Homologous to Linear Epitopes of Ara h 1, 2 and 3 in Relation to Clinical Reactivity. Int Arch Allergy Immunol. 2012; 157: 238-245.
- Roux K et al. Tree nut allergens. Int Arch Allergy Immunology 2003; 131: 234-244.

**Cashew IgG**

**Interpretation:**

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

**Cashew, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cashew
- Defining the allergen responsible for eliciting signs and symptoms
- Identifying allergens:
  - Responsible for allergic disease and/or anaphylactic episode
  - To confirm sensitization prior to beginning immunotherapy
  - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**CASPsz**

**CASPz Gene, Full Gene Analysis, Varies**

**Clinical Information:** The extracellular G-protein-coupled calcium-sensing receptor (CASPz) is an essential component of calcium homeostasis. CASPz is expressed at particularly high levels in the parathyroid glands and kidneys. It forms stable homodimeric cell-membrane complexes, which signal upon binding of extracellular calcium ions (Ca++). In the parathyroid glands, this results in downregulation of gene expression of the main short-term regulator of calcium homeostasis, parathyroid hormone (PTH), as well as diminished secretion of already synthesized PTH. At the same time, renal calcium excretion is upregulated and sodium chloride excretion is downregulated. Ca(++) binding to CASPz is highly cooperative within the physiological Ca(++) concentration range, leading to a steep dose-response curve, which results in tight control of serum calcium levels. To date, over 100 different alterations in the CASPz gene have been described. Many of these cause diseases of abnormal serum calcium regulation. Inactivating mutations result in undersensing of Ca(++) concentrations and consequent PTH overproduction and secretion. This leads to either familial hypocalciuric hypercalcemia (FHH) or neonatal severe primary hyperparathyroidism (NSPHT), depending on the severity of the functional impairment. Except for a very small percentage of cases with no apparent CASPz mutations, FHH is due to heterozygous inactivating CASPz mutations. Serum calcium levels are mildly-to-moderately elevated. PTH is within the reference range or modestly elevated, phosphate is normal or slightly low, and urinary calcium excretion is low for the degree of hypercalcemia. Unlike patients with primary hyperparathyroidism (PHT), which can be difficult to distinguish from FHH, the majority of FHH patients do not seem to suffer any adverse long-term effects from hypercalcemia and elevated PTH levels. They should, therefore, generally not undergo parathyroidectomy. NSPHT is usually due to homozygous or compound heterozygous inactivating CASPz mutations, but can occasionally be caused by dominant-negative heterozygous mutations. The condition presents at birth, or shortly thereafter, with severe hypercalcemia requiring urgent parathyroidectomy. Activating mutations lead to oversensing of Ca(++), resulting in suppression of PTH secretion and consequently hypoparathyroidism. All activating mutations described are functionally dominant and disease inheritance is therefore autosomal dominant. However, sporadic cases also occur. Autosomal dominant hypoparathyroidism caused by CASPz mutations may account for many cases of idiopathic hypoparathyroidism. Disease severity depends on the degree of gain of function, spanning the spectrum from mild hypoparathyroidism, which is diagnosed incidentally, to severe and early onset disease. In addition, while the majority of patients suffer only from hypoparathyroidism, a small subgroup with...
extreme gain of function mutations suffer from concomitant inhibition of renal sodium chloride transport. These individuals may present with additional symptoms of hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypomagnesemia, consistent with type V Bartter syndrome.

**Useful For:** Establishing a diagnosis of familial hypocalciuric hypercalcemia As part of the workup of some patients with primary hyperparathyroidism Establishing a diagnosis of neonatal severe primary hyperparathyroidism Establishing a diagnosis of autosomal dominant hypoparathyroidism As part of the workup of idiopathic hypoparathyroidism As part of the workup of patients with Bartter syndrome

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided


**Cat Epithelium, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cat epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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Reference values apply to all ages.


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**COMTQ**

**Catechol-O-Methyltransferase (COMT) Genotype, Varies**

**Clinical Information:** Catechol-O-methyltransferase (COMT) is involved in phase II (conjugative) metabolism of catecholamines and catechol drugs, such as dopamine, as well as the catechol-estrogens. COMT transfers a donor methyl-group from S-adenosylmethionine to acceptor hydroxy groups on catechol structures (aromatic ring structures with vicinal hydroxy-groups).(1) Bioactive catecholamine metabolites are metabolized by COMT in conjunction with monoamine oxidase (MAO):

- Norepinephrine is methylated by COMT forming normetanephrine. -Epinephrine is methylated by COMT forming metanephrine. -Dopamine is converted to homovanillic acid through the combined action of MAO and COMT. Parkinsonism patients receiving levodopa (L-Dopa) therapy are frequently also prescribed a COMT inhibitor to minimize metabolism of L-Dopa by COMT, thereby prolonging L-Dopa action. COMT is also involved in the inactivation of estrogens. Estradiol can be hydroxylated forming the catechol estrogens 2-hydroxyestradiol and 4-hydroxyestradiol.(2) These hydroxylated estradiols are methylated by COMT, forming the corresponding methoxyestradiols. The gene encoding COMT is transcribed from alternative promoters to produce 2 forms of the enzyme, a soluble short form of the enzyme and a membrane-bound long form. Variants in the COMT gene are therefore designated in the literature by the position of the amino acid change in both the short and long form of the enzyme. A single nucleotide variant (SNV) in exon 4 of the gene produces an amino acid change from valine to methionine (Val108/158Met). The presence of methionine at this position reduces the maximum activity of the variant enzyme by 25% and also results in significantly less immunoreactive COMT protein, resulting in a 3-fold to 4-fold decrease in activity compared to wild type (valine at this position). This variant has been associated with prediction of response and risk of relapse when using nicotine replacement therapy for smoking cessation.(3) The following information outlines the relationship between the polymorphism detected in this assay and the effect on the activity of the enzyme produced by that allele: Amino acid change cDNA nucleotide change (NM_000754.3) Effect on enzyme activity/metabolism None (wild-type) None (wild type) Normal activity p.Val158Met (known as Val108Met) c.472G>A Reduced activity

**Useful For:** Prediction of response to nicotine replacement therapy for smoking cessation Investigation of inhibitor dosing for decreasing levodopa metabolism Research use for assessing estrogen metabolism

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

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**CATU 9276**

**Catecholamine Fractionation, Free, 24 Hour, Urine**

**Clinical Information:** The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and play crucial roles in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but also differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. They are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma, a potentially curable tumor of catecholamine producing cells of the adrenal medulla, or less commonly of sympathetic ganglia (paraganglioma), urine catecholamine levels may be elevated. This results in episodic or sustained hypertension and often in intermittent attacks of palpititations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea ("spells"). Elevations of the urine levels of 1 or several of the catecholamines also may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines, or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

**Useful For:** An auxiliary test to fractionated plasma and urine metanephrine measurements in the diagnosis of pheochromocytoma and paraganglioma. An auxiliary test to urine vanillylmandelic acid and homovanillic acid determination in the diagnosis and follow-up of patients with neuroblastoma and related tumors.

**Interpretation:** Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma. PMET / Metanephrines, Fractionated, Free, Plasma (the most sensitive assay) and/or METAF / Metanephrines, Fractionated, 24 Hour, Urine (almost as sensitive and highly specific) are the recommended first-line laboratory tests for pheochromocytoma. However, urine catecholamine measurements can still be useful in patients whose plasma metanephrines or urine metanephrines measurements do not completely exclude the diagnosis. In such cases, urine catecholamine specimens have an 86% diagnostic sensitivity when cut-offs of >80 mg/24 hour for norepinephrine and >20 mg/24 hour for epinephrine are employed. Unfortunately, the specificity of these cut-off levels for separating tumor patients from other patients with similar symptoms is only 88%. When more specific (98%) decision levels of >170 mg/24 hours for norepinephrine or >35 mg/24 hours for epinephrine are used, the assay's sensitivity falls to about 77%. Diagnosis of Neuroblastoma: Vanillylmandelic acid,
homovanillic acid, and sometimes urine catecholamine measurements on spot urine or 24-hour urine are the mainstay of biochemical diagnosis and follow-up of neuroblastoma; 1 or more of these tests may be elevated.

**Reference Values:**

**NOREPINEPHRINE**

- <1 year: <11 mcg/24 hours
- 1 year: 1-17 mcg/24 hours
- 2-3 years: 4-29 mcg/24 hours
- 4-6 years: 8-45 mcg/24 hours
- 7-9 years: 13-65 mcg/24 hours
- ≥10 years: 15-80 mcg/24 hours

**EPINEPHRINE**

- <1 year: <2.6 mcg/24 hours
- 1 year: <3.6 mcg/24 hours
- 2-3 years: <6.1 mcg/24 hours
- 4-9 years: 0.2-10.0 mcg/24 hours
- 10-15 years: 0.5-20.0 mcg/24 hours
- ≥16 years: <21 mcg/24 hours

**DOPAMINE**

- <1 year: <86 mcg/24 hours
- 1 year: 10-140 mcg/24 hours
- 2-3 years: 40-260 mcg/24 hours
- ≥4 years: 65-400 mcg/24 hours

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

**Clinical References:**


**CATP**

**Catecholamine Fractionation, Free, Plasma**

**Clinical Information:** The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and also play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap, but also differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. The catecholamines are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss,
hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine-producing cells of the adrenal medulla), or less commonly of sympathetic ganglia (paraganglioma), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of 1 or several of the catecholamines may also be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction or failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

**Useful For:** Diagnosis of pheochromocytoma and paraganglioma, as an auxiliary test to fractionated plasma and urine metanephrine measurements (plasma metanephrine is the preferred test for this diagnosis) Diagnosis and follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction or failure or autonomic neuropathy

**Interpretation:** Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated, but only secreted during a "spell." By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can still be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if drawn during a "spell," have a 90% to 95% diagnostic sensitivity when cutoffs of >750 pg/mL for norepinephrine and >110 pg/mL for epinephrine are employed. A lower value during a "spell," particularly when plasma or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not good for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2,000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay’s sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements on spot urine or 24-hour urine are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be observed in these tumors. Diagnosis of Autonomic Dysfunction or Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction or failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels, or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

**Reference Values:**

**NOREPINEPHRINE**
- Supine: 70-750 pg/mL
- Standing: 200-1,700 pg/mL

**EPINEPHRINE**
- Supine: < or =111 pg/mL
- Standing: < or =141 pg/mL

**DOPAMINE**
- <30 pg/mL (no postural change)

Catfish (Siluriformes spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 >100 Very High Positive

Reference Values:
<0.35 kU/L

Cathartic Laxatives Profile, Stool

Interpretation: Magnesium: Magnesium concentrations in stool water above the normal levels of 0.7-1.2 mg/mL have been indicative of surreptitious abuse of magnesium containing laxatives. NMS Labs Calculated Normal: approximately 0.5-10 mg/g (Based on the reported range of magnesium eliminated per day in stool and the range of stool mass per day in adults). Not for clinical diagnostic purposes. Phosphorus: Phosphorus concentration in stool water averaged 1.8 +/- 0.3 mg/mL (ranged from 0.3-4.2 mg/mL) following administration of 105 mmol of sodium phosphate. NMS Labs calculated normal: approximately 1.4-22 mg/g (Based on the reported range of phosphorus eliminated per day in stool and the range of stool mass per day in adults)/ Not for clinical diagnostic purposes. Specimens for elemental testing should be collected in certified metal-free containers. Elevated results of elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen.

Reference Values:
Reporting limit determined each analysis.
Units: mg/g

Cathepsin K Immunostain, Technical Component Only

Clinical Information: Cathepsin K is a protease whose expression is driven by microphthalmia transcription factor (MITF) in osteoclasts. Cathepsin K is also expressed in renal perivascular epithelioid cell neoplasms (PEComas), alveolar soft part sarcoma, and most MiT family translocation -renal cell carcinomas. This includes most transcription factor EB- (TFEB) rearranged renal cell carcinomas, those with amplifications of TFEB, and renal cell carcinomas that harbor various TFE3 gene fusions.

Useful For: A marker of myeloid lineage

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control
tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**FCAF G**

**Cauliflower IgG**

**Interpretation:**

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

**CALFL**

**Cauliflower, IgE, Serum**

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

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

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

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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### CD10 Immunostain, Technical Component Only

**Clinical Information:** CD10 is a cell surface glycoprotein present on bone marrow B precursors (hematogones) and myeloid cells (including neutrophils), follicle center B cells, and a subset of follicular T helper cells. CD10 is also expressed in the brush border of the upper part of the intestinal tract, bile canaliculi, kidney (glomerular and proximal tubular cells), pulmonary alveolar cells, myoepithelial cells of breast, prostate glandular cells, placental trophoblastic cells, endometrial stromal cells, some endothelial cells, and a minority of (myo-)fibroblasts (stromal cells). CD10 is most useful in the diagnosis of B-precursor-acute lymphoblastic leukemia, Burkitt lymphoma, and lymphomas of follicle cell center origin (follicular lymphoma, subset of large B-cell lymphomas).

**Useful For:** Phenotyping leukemias and lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
3. Lloyd J, Owens S: CD10 immunohistochemistry stains enteric mucosa, but negative staining is unreliable in the setting of active enteritis. Mod Pathol. 2011;24:1627-1632. doi: 10.1038/modpathol.2011.122

### CD103 Immunostain, Technical Component Only

**Clinical Information:** CD103, also known as integrin alpha E, is an integrin subunit protein, which is widely expressed on T cells. CD103 is a useful diagnostic tool in the diagnosis of hairy cell leukemia.

**Useful For:** Aids in the diagnosis of hairy cell leukemia and marginal zone lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control
tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD11c Immunostain, Technical Component Only**

**Clinical Information:** CD11c is a member of the leukocyte specific integrin family, involved in adherence to activated endothelial cells and complement-mediated phagocytosis. CD11c is normally expressed on histiocytes and monocytes, and weakly expressed on granulocytes. CD11c is also expressed on certain B cell neoplasms, including hairy cell leukemia and splenic marginal zone lymphoma.

**Useful For:** Aiding in the diagnosis of hematological malignancies and identification of cells of the macrophage/dendritic cell lineage within tissues

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD123 Immunostain, Technical Component Only**

**Clinical Information:** In normal lymphoid tissues, CD123 is expressed in plasmacytoid monocytes and mast cells in interfollicular regions. In bone marrow, it is expressed in hematopoietic precursors, mast cells, and megakaryocytes. CD123 is part of the IL3 receptor complex, involved in cellular growth and differentiation. Certain reactive lymph nodes show increased numbers of plasmacytoid monocytes, eg, Kikuchi lymphadenitis. CD123 is characteristically expressed in blastic plasmacytoid dendritic cell neoplasm, aiding in its distinction from acute monocytic leukemia.

**Useful For:** Marker of plasmacytoid monocytes, mast cells, and megakaryocytes

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
CD13 Immunostain, Technical Component Only

Clinical Information: CD13 (cluster of differentiation 13) plays roles in peptide metabolism (brush border membranes of small intestine, renal proximal tubules, and placenta), cell growth and differentiation, and phagocytosis. CD13 is normally expressed on myeloid lineage cells, including granulocytes and monocytes. It is also expressed on non-hematolymphoid cells including endothelial cells and fibroblasts, and is present in a soluble form in plasma. This immunostain may be useful as a marker of myeloid lineage in acute leukemias.

Useful For: A marker of myeloid lineage

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD138 (Syndecan) Immunostain, Technical Component Only

Clinical Information: CD138 is expressed on plasma cells and can be useful in the diagnosis of plasma cell neoplasms. Epithelial cells and endothelial cells may also express CD138. In normal tonsil tissue, CD138 strongly stains the membranes of mature plasma cells and squamous epithelial cells.

Useful For: Marker of plasma cells and squamous epithelial cells

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

CD14 Immunostain, Technical Component Only

Clinical Information: CD14 is a glycosylphosphatidylinositol-linked glycoprotein that is preferentially expressed by mature cells of monocytic lineage (monocytes, macrophages, Langerhans cells) and follicular dendritic cells. Neutrophils exhibit lower levels of expression. This antibody may be useful as a marker of histiocytic/monocytic lineage in acute leukemias.

Useful For: A marker of histiocytic and monocytic lineage and follicular dendritic cells

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD15 Immunostain, Technical Component Only

Clinical Information: CD15 is expressed in granulocytes and can be expressed in malignant lymphomas and acute myeloid leukemias. The Reed-Sternberg cells of classical Hodgkin lymphoma are characteristically positive for CD15 and CD30.

Useful For: Phenotyping leukemias and lymphomas

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD163 Immunostain, Technical Component Only

Clinical Information: CD163 (cluster of differentiation 163) is a scavenger receptor for the hemoglobin-haptoglobin complex. CD163 is a marker of monocytic/histiocytic lineage, expressed late in maturation. It has superior specificity for monocytic/histiocytic lineage compared to CD68. In normal lymphoid tissues, staining of histiocytes in the paracortex and follicle center (tingible body macrophages) is seen. CD163 is usually negative in immature monocytic/histiocytic tumors (acute myeloid leukemia with monocytic differentiation).
**Useful For:** Identification of cells of monocytic/histiocytic lineage, expressed late in maturation

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD19 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** CD19 is expressed by normal and neoplastic B cells but is not expressed by T cells, monocytes, or granulocytes. CD19 protein appears early during B-cell maturation and is found during all stages of B-cell maturation, including plasma cells. CD19 is useful as an additional marker of B cell lineage in leukemias and lymphomas. Expression of CD19 may be seen in some acute myeloid leukemias.

**Useful For:** Identification of normal and neoplastic B cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD19 Immunostain, Technical Component Only**

**Clinical Information:** CD19 is expressed by normal and neoplastic B cells but is not expressed by T cells, monocytes, or granulocytes. CD19 protein appears early during B-cell maturation and is found during all stages of B-cell maturation, including plasma cells. CD19 is useful as an additional marker of B cell lineage in leukemias and lymphomas. Expression of CD19 may be seen in some acute myeloid leukemias.

**Useful For:** Identification of normal and neoplastic B cells

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain.Â If an interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing...
appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD1A**

**CD1a Immunostain, Technical Component Only**

**Clinical Information:** CD1a is a membrane surface glycoprotein that is expressed in Langerhans cells and immature T cells. CD1a expression is useful in phenotyping acute lymphoblastic leukemia/lymphoma of T-cell lineage and in the diagnosis of Langerhans cell histiocytosis.

**Useful For:** Marker of Langerhans cells and immature T cells

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. (no pathologist interpretation is performed). If diagnostic consultation by a pathologist interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD2B**

**CD2 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** CD2 is a pan T-cell antigen, expressed on normal and neoplastic T cells and natural killer cells. In normal tonsil, the T cells predominate in interfollicular regions. CD2 immunostaining is useful in determining T-cell lineage in cases of T-cell lymphoma.

**Useful For:** Determining T-cell lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

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**CD2 Immunostain, Technical Component Only**

**Clinical Information:** CD2 is a pan T-cell antigen that is expressed on normal and neoplastic T cells and natural killer cells. CD2 immunostaining is useful in determining T-cell lineage in cases of T-cell lymphoma.

**Useful For:** Determining T-cell lineage

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. (no pathologist interpretation is performed). If diagnostic consultation by a pathologist interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CD20 Cell Expression Evaluation, Varies**

**Clinical Information:** Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

**Useful For:** Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD20 Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

**Interpretation:** The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

**Reference Values:**
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.


**CD20I**

**CD20 Immunostain, Technical Component Only**

**Clinical Information:** CD20 is a phosphorylated protein preferentially expressed by mature B lymphocytes. CD20 is not expressed by most normal plasma cells. It is one of the most specific B-cell lineage-associated antigens used in the diagnosis of B-cell lymphomas.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD20B**

**CD20 on B Cells, Blood**

**Clinical Information:** CD20 (cluster of differentiate 20) is a protein that is expressed on the surface of B cells, starting at the pre-B cell stage and also on mature B cells in the bone marrow and in the periphery. CD20 is not expressed on hematopoietic stem cells, pro-B cells, or normal plasma cells.(1) Plasmablasts and stimulated plasma cells may express CD20.(2) CD20 is generally co-expressed on B cells with CD19, another B-cell differentiation marker. CD20 appears to play a role in B-cell development, differentiation, B-cell receptor (BCR) signaling, and cell-cycle initiation events.(3) CD20 is not shed from the surface of B cells and does not internalize on binding with anti-CD20 antibody, nor is it typically present as a soluble free antigen in circulation.(3) Certain primary humoral immunodeficiencies, such as X-linked agammaglobulinemia and autosomal recessive agammaglobulinemia, are characterized by a complete absence or profound reduction of peripheral B cells, expressing both CD20 and CD19 (another B-cell differentiation marker). Variants in the CD19 gene have been shown to be associated with a primary humoral immunodeficiency, sometimes classified as common variable immunodeficiency (CVID).(4) This defect accounts for less than 1% to 2% of CVID patients and appears to be inherited as an autosomal recessive defect.(4) Since these patients have normal numbers of B cells with absent CD19 expression on the cell surface (4), CD20 can be used as a marker to help identify these patients. A contrasting situation exists for patients receiving rituximab, ofatumumab, and other anti-CD20 monoclonal antibodies that are used to treat certain cancers, autoimmune diseases, or for B-cell depletion.

Current as of June 14, 2021 12:13 pm CDT
to prevent humoral rejection in positive crossmatch renal transplantation. These agents block available
CD20-binding sites and, therefore, the antibody used for this flow cytometric assay cannot recognize the
CD20 molecule on B cells. The concomitant use of the CD19 marker provides information on the extent
of B-cell depletion when using this particular treatment strategy. The absolute counts of lymphocyte
subsets are known to be influenced by a variety of biological factors, including hormones, the
environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have
demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+
B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer
cell counts, on the other hand, are constant throughout the day.(5) Circadian variations in circulating
T-cell counts have been shown to be negatively correlated with plasma cortisol concentration,(6-8) In
fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive
versus effector CD4 and CD8 T cells.(6) It is generally accepted that lower CD4 T-cell counts are seen in
the morning compared with the evening (9), and during summer compared to winter.(10) These data,
therefore, indicate that timing and consistency in timing of blood collection is critical when serially
monitoring patients for lymphocyte subsets.

**Useful For:** Evaluation of CD19 deficiency in patients with a suspected CD19 deficiency (humoral
immunodeficiency) Confirming complete absence of B cells in suspected primary humoral
immunodeficiencies using both CD19 and CD20 markers Assessing therapeutic B-cell depletion
quantitatively (absolute counts of cells/mcL) in any clinical context, including malignancies,
autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and membranous
glomerulonephritis among others, and treatment or prevention of acute humoral rejection in positive
crossmatch renal transplant recipients This test is not useful for assessing whether B cells express the
target molecule (CD20) in the context of initiating therapeutic monoclonal anti-CD20 antibody therapy
(rituximab, ofatumumab, and tositumomab) for any of the hematological malignancies, or in other
clinical contexts, such as autoimmunity, instead order CEE20 / CD20 Cell Expression Evaluation,
Varies.

**Interpretation:** The presence of CD20+ B cells with corresponding absence of CD19 staining in
individuals not receiving anti-CD20 monoclonal antibody treatment or with clinical features of variable
primary humoral immunodeficiency may suggest an underlying CD19 deficiency, which should be
further evaluated. Absence of both CD20 and CD19 markers on B cells in blood from individuals not on
anti-CD20 monoclonal antibody treatment is consistent with complete mature and immature peripheral
B-cell depletion, which may be due to an underlying primary immunodeficiency. Patients receiving
B-cell depleting therapy with anti-CD20 antibodies can show unusual populations of B cells on
reconstitution that express either CD19 or CD20 due to a phenomenon known as trogocytosis.

**Reference Values:**

- **%CD19 B CELLS**
  - > or =19 years: 4.6-22.1%

- **CD19 ABSOLUTE**
  - > or =19 years: 56.6-417.4 cells/mcL

- **%CD20 B CELLS**
  - > or =19 years: 5.0-22.3%

- **CD20 ABSOLUTE**
  - > or =19 years: 74.4-441.1 cells/mcL

- **CD45 ABSOLUTE**
  - 18-55 years: 0.99-3.15 thou/mcL
  - >55 years: 1.00-3.33 thou/mcL

**Clinical References:** 1. Nadler LM, Ritz J, Hardy R, et al: A unique cell-surface antigen
Avet-Loiseau H, Garand R, et al: CD20 is associated with a small mature plasma cell morphology and

**CD21 Immunostain, Technical Component Only**

**Clinical Information:** CD21 strongly stains the cytoplasm and membranes of the follicular dendritic cells and the membranes of a subset of the mantle zone lymphocytes. Follicular dendritic cells form a basket-weave meshwork in the germinal centers of lymphoid follicles, where they present antigens to B cells. Diagnostically, CD21 may be useful to support a diagnosis of follicular dendritic cell sarcoma, or to confirm the presence of lymphoid follicles.

**Useful For:** Identification of follicular dendritic cells and a subset of mantle zone lymphocytes

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD22 Immunostain, Technical Component Only**

**Clinical Information:** CD22 is expressed on B lymphocytes. It can be used as an alternative B-cell marker to CD20 or CD79a. Diagnostically, CD22 is useful to confirm B-cell lineage in malignant lymphomas.

**Useful For:** Determining B-cell lineage

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:** 1. Kreitman RJ, Arons E: Update on hairy cell leukemia. Clin Adv Hematol
**CD23 Immunostain, Technical Component Only**

**Clinical Information:** CD23 strongly stains the cytoplasm and membranes of follicular dendritic cells and the membranes of a subset of follicular mantle zone B-lymphocytes. Typically, B-cell small lymphocytic lymphoma/chronic lymphocytic leukemias are CD5 positive and CD23 positive, while mantle cell lymphoma is CD5 positive and CD23 negative. Antibodies to CD23 are diagnostically useful in the classification of low-grade B-cell lymphomas.

**Useful For:** Identification of follicular dendritic cells Classification of low-grade B-cell lymphomas

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If an interpretation is required, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CD25 Immunostain, Technical Component Only**

**Clinical Information:** CD25 is the receptor for IL2 and is expressed on activated T cells, B cells, and macrophages. It will stain only scattered cells in normal tonsil. CD25 is expressed in certain types of B-cell lymphoma (hairy cell leukemia) and T-cell lymphoma (adult T-cell lymphoma/leukemia [ATLL]). An anti-CD25 therapy can be used in patients who have lymphomas that express CD25.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**CD273 (PD-L2) Immunostain, Technical Component Only**

**Clinical Information:** CD273 also known as programmed cell death 1-ligand 2 (PD-L2) regulates T-cell activation in addition to immune responses and is a member of the B7 family of cell surface ligands. CD273 (PD-L2) is useful in the distinction of primary mediastinal large B cell lymphoma (PMBL) from diffuse large B cell lymphoma (DLBCL).

**Useful For:** Differentiation of primary mediastinal large B-cell lymphoma (PMBL) from diffuse large B cell-lymphoma (DLBCL)

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation of second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic in Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD279 (PD-1) Immunostain, Technical Component Only**

**Clinical Information:** CD279 (cluster of differentiation 279 or programmed cell death 1: PD-1) is an immunoregulatory receptor highly expressed by follicular T helper cells, and its expression has also been shown in the neoplastic counterpart of this T-cell subset, angioimmunoblastic T-cell lymphoma. This molecule interacts with PD-L1 (B7H1) expressed on follicular dendritic cells and other cell types, which serves to attenuate T-cell activation. In the appropriate histologic context, a background rich in CD279-positive T cells can support a diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma.

**Useful For:** Identification of follicular T helper cells Phenotyping of angioimmunoblastic T-cell lymphoma

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
**CD3 Immunostain, Technical Component Only**

**Clinical Information:** CD3 (cluster of differentiation 3) is part of the T-cell antigen receptor complex found on the surface of T lymphocytes. In paraffin sections, antibodies to CD3 will also react with a subset of natural killer cells that express the cytoplasmic epsilon chain of CD3. In normal tonsil, the T cells predominate in the interfollicular regions. Diagnostically, antibodies to CD3 are useful in demonstrating T-cell lineage of malignant lymphomas.

**Useful For:** Demonstrating T-cell lineage

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD30 Immunostain, Technical Component Only**

**Clinical Information:** CD30 is a member of the tumor necrosis factor receptor (TNF-R) superfamily. Expression of CD30 can also be seen in embryonal carcinomas, malignant melanomas, mesenchymal tumors, and activated T and B lymphocytes and plasma cells. Reed-Sternberg cells of classic Hodgkin lymphoma, as well as the neoplastic cells of anaplastic large cell lymphoma, express CD30.

**Useful For:** Identification of CD30 expression in a variety of neoplasms

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD303 (BDCA-2) Immunostain, Technical Component Only**

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**CD303 (BDCA-2) Immunostain, Technical Component Only**

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**CD303 (BDCA-2) Immunostain, Technical Component Only**
Clinical Information: CD303 (BDCA-2) is a highly specific marker for normal and neoplastic plasmacytoid dendritic cells (PDC) and may be useful as a specific marker for the diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN). CD303 (BDCA-2) is expressed in the cytoplasm/membrane of plasmacytoid dendritic cells.

Useful For: The diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD31 ImmunoStain, Technical Component Only

Clinical Information: CD31 (cluster of differentiation 31) is expressed on endothelial cells, showing some membrane and occasional cytoplasmic staining. It is not expressed on discontinuous endothelium (eg, splenic red pulp). It is also expressed on megakaryocytes, histiocytes, plasma cells, and T-cell subsets. Tonsil sections will exhibit endothelial positivity in vessels primarily located in connective tissue areas around follicles and near the epithelial borders. Diagnostically, CD31 expression can confirm a diagnosis of angiosarcoma, a neoplasm of endothelial cells.

Useful For: Marker of endothelial cells

Interpretation: This test does not include pathologist interpretation: only technical performance of the stain. If an interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD33 Immunostain, Technical Component Only

Clinical Information: CD33 is a transmembrane protein that is a member of the sialic acid-binding immunoglobulin-like lectin (Siglec) family. The exact function of CD33 is not known, but it may be involved in cell to cell adhesion. It is not expressed on hematopoietic stem cells but is expressed on maturing myelomonocytic cells. As granulocytes mature, there is progressive down regulation of CD33. Monocytes and macrophage/histiocytic cells maintain strong expression of CD33. In normal bone
marrow, weak to moderate CD33 staining is seen on granulocytic and monocytic precursors, with strong staining in scattered mast cells. CD33 staining is useful for diagnosis of myeloid neoplasms and classification of acute leukemias. A therapeutic antibody targeting CD33 (gemtuzumab/Myelotarg) is available.

**Useful For:** Classification of myeloid neoplasms and acute leukemias

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD34 Immunostain, Technical Component Only**

**Clinical Information:** CD34 is 115 kDa membrane associated antigen found on human hematopoietic progenitor cells and vascular endothelial cells. In normal tonsil sections, antibodies to CD34 strongly stain vascular endothelial cells. CD34 is used as a marker of immaturity in the setting of acute myeloid leukemia or B lymphoblastic leukemia. It is also useful in the diagnosis of gastrointestinal stromal tumors, solitary fibrous tumors, and angiosarcomas.

**Useful For:** A marker of immaturity in the setting of acute myeloid leukemia or B lymphoblastic leukemia The diagnosis of gastrointestinal stromal tumors, solitary fibrous tumors, and angiosarcomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD35 Immunostain, Technical Component Only**

**Clinical Information:** CD35 (cluster of differentiation 35) stains the membrane and cytoplasm of follicular dendritic cells and granulocytes. Follicular dendritic cells form a basketweave meshwork in
the germinal centers of lymphoid follicles, where they present antigens to B cells. CD35 is useful in the diagnosis of follicular dendritic-cell sarcoma.

**Useful For:** Identification of follicular dendritic cells and granulocytes

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD38 Immunostain, Technical Component Only**

**Clinical Information:** CD38 (cluster of differentiation 38) is expressed in a variety of cell types including hematopoietic precursors, plasma cells, germinal center B cells (weakly), a subset of T and NK cells, erythrocytes, platelets, prostatic epithelium, and smooth and striated muscle cells. Its expression maybe useful in the diagnosis of lymphoproliferative and plasma cell proliferative disorders.

**Useful For:** Classification of lymphoproliferative and plasma cell proliferative disorders

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD4 Count for Immune Monitoring, Blood**

**Clinical Information:** Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/µL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 co-receptors. The absolute counts of lymphocyte subsets are known to be
influenced by a variety of biological factors, including hormones, the environment, and temperature. The
studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T-lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

**Useful For:** Serial monitoring of CD4 T cell count in HIV-positive patients Useful for follow-up and
diagnostic evaluation of primary cellular immunodeficiencies, including severe combined
immunodeficiency T-cell immune monitoring following immunosuppressive therapy for
transplantation, autoimmunity, and other immunological conditions where such treatment is utilized
Assessment of T-cell immune reconstitution post hematopoietic cell transplantation Early screening of
gross quantitative anomalies in T cells in infection or malignancies

**Interpretation:** HIV treatment guidelines from the US Department of Health and Human Services
and the International Antiviral Society USA Panel recommend antiviral treatment in all patients with
HIV infection, regardless of CD4 T-cell count.(7,8) Additionally, antibiotic prophylaxis for
Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with
CD4 counts below 200 cells/mcL.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:** 1. Carmichael KF, Abayomi A: Analysis of diurnal variation of lymphocyte
subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on
Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood
al: Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal
Simms TE, Gray GC, et al: Sources of variability in repeated T-helper lymphocyte counts from HIV
1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS
Transfusion 1994;34:512-516 7. US Department of Health and Human Services: Guidelines for the use
of antiretroviral agents in HIV-1-infected adults and adolescents. Available at
adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA
2012;308:387-402
these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan T-cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

**Useful For:** Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of T-cell immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in T cells in infection or malignancies

**Interpretation:** HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(7,8) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with a CD4 count below 200 cells/mL.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**
CD4 Immunostain, Technical Component Only

**Clinical Information:** CD4 (cluster of differentiation 4) is expressed on a subset of T cells (T helper cells), histiocytes, and monocytes. In normal tonsil, the T cells predominate in interfollicular regions. This immunostain is also used to support T cell or histiocytic lineage in hematolymphoid neoplasms.

**Useful For:** Identification of T helper cells, histiocytes, and monocytes

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD4 T-Cell Recent Thymic Emigrants, Blood

**Clinical Information:** Naive T-cells are generated in the thymus and exported to peripheral blood to form the peripheral T-cell repertoire. There is a decrease in naive T cells derived from the thymus with age due to age-related decline in thymic output. Recent thymic emigrants (RTEs) typically refers to those populations of naive T cells that have not diluted their TREC copies (T-cell receptor excision circles) by homeostatic or antigen-driven cell division. Naive T cells can be long-lived in the periphery and postpuberty, and in adults, peripheral T-cell homeostasis is maintained by a balance of thymic output and peripheral T-cell expansion and this proportion changes with age. In infants and prepubertal children, the T-cell repertoire is largely maintained by thymic-derived naive T cells. RTEs express TREC's indicative of naive T cells derived from the thymus.(1) In the CD4 T-cell compartment it has been shown that naive CD45RA+ T cells coexpressing CD31 had a higher frequency of TREC compared to T cells lacking CD31.(2) The higher proportion of TREC+ naive T cells indicate a more recent thymic ontogeny since TRECs can be diluted by cell division (since they are extrachromosomal). It has been shown that CD31+CD4+ T cells continue to possess a relatively higher proportion of TREC despite an age-related 10-fold reduction after the neonatal period.(3) CD4 RTEs (CD31+CD4+CD45RA+) have longer telomeres and higher telomerase activity, which, along with the increased frequency of TREC positivity suggests a population of T cells with low replicative history.(3) The same study has also shown that CD31+ CD4+ T cells are an appropriate cell population to evaluate thymic reconstitution in lymphopenic children posthematopoietic cell transplant.(3) A Mayo study (unpublished) shows that the CD31 marker correlates with TREC-enriched T cells across the spectrum of age and correlates with thymic recovery in adults after autologous hematopoietic cell transplantation.(4) CD31+ CD4 RTEs have also been used to evaluate T-cell homeostatic anomalies in patients with relapsing-remitting multiple sclerosis.(5) For patients with DiGeorge syndrome (DGS)--a cellular immunodeficiency associated with other congenital problems including cardiac defects, facial dysmorphism, hypoparathyroidism, and secondary hypocalcemia, and chromosome 22q11.2 deletion (in a significant proportion of patients)--measurement of thymic function provides valuable information on...
the functional phenotype, ie, complete DGS (associated with thymic aplasia in a minority of patients) or partial DGS (generally well-preserved thymic function seen in the majority of patients). Thymus transplants have been performed in patients with complete DGS, but are typically not required in partial DGS. There can be change in peripheral T-cell counts in DGS patients with age.

**Useful For:** Evaluating thymic reconstitution in patients following hematopoietic cell transplantation, chemotherapy, immunomodulatory therapy, and immunosuppression Evaluating thymic output in patients with DiGeorge syndrome or other cellular immunodeficiencies Assessing the naïve T-cell compartment in a variety of immunological contexts (autoimmunity, cancer, immunodeficiency, and transplantation) Identification of thymic remnants postthymectomy for malignant thymoma or as an indicator of relapse of disease (malignant thymoma) or other contexts of thymectomy

**Interpretation:** The absence or reduction of CD31+CD4 recent thymic emigrants (RTEs) generally correlates with loss or reduced thymic output and changes in the naïve CD4 T-cell compartment, especially in infancy and prepubertal children. The CD4RTE result has to be interpreted more cautiously in adults due to age-related decline in thymic function and correlated with total CD4 T cell count and other relevant immunological data. CD4 RTEs measured along with TREC (TREC / T-Cell Receptor Excision Circles (TREC) Analysis, Blood) provides a comprehensive assessment of thymopoiesis, but should not be used in adults over the sixth decade of life as clinically meaningful information on thymic function is limited in the older population due to a physiological decline in thymic activity. To evaluate immune reconstitution or recovery of thymopoiesis post-T-cell depletion due to posthematopoietic cell transplant, immunotherapy, or other clinical conditions, it is helpful to systematically (serially) measure CD4RTE, and TREC copies in the appropriate age groups.

**Reference Values:**

**CD4 ABSOLUTE**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month-17 years</td>
<td>153-1,745 cells/mcL</td>
</tr>
<tr>
<td>Males</td>
<td>18-70 years</td>
<td>290-1,175 cells/mcL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &lt;30 days of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &gt;70 years of age.</td>
</tr>
<tr>
<td>Females</td>
<td>1 month-17 years</td>
<td>582-1,630 cells/mcL</td>
</tr>
<tr>
<td></td>
<td>18-70 years</td>
<td>457-1,766 cells/mcL</td>
</tr>
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<td>Reference values have not been established for patients that are &lt;30 days of age.</td>
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<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &gt;70 years of age.</td>
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</tbody>
</table>

**CD4 RTE %**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month-17 years</td>
<td>19.4-60.9%</td>
</tr>
<tr>
<td>Males</td>
<td>18-25 years</td>
<td>6.4-51.0%</td>
</tr>
<tr>
<td></td>
<td>26-55 years</td>
<td>6.4-41.7%</td>
</tr>
<tr>
<td></td>
<td>&gt; or =56 years</td>
<td>6.4-27.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &lt;30 days of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &gt;70 years of age.</td>
</tr>
<tr>
<td>Females</td>
<td>1 month-17 years</td>
<td>25.8-68.0%</td>
</tr>
<tr>
<td></td>
<td>18-25 years</td>
<td>6.4-51.0%</td>
</tr>
<tr>
<td></td>
<td>26-55 years</td>
<td>6.4-41.7%</td>
</tr>
<tr>
<td></td>
<td>&gt; or =56 years</td>
<td>6.4-27.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &lt;30 days of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &gt;70 years of age.</td>
</tr>
</tbody>
</table>

**CD4 RTE ABSOLUTE**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month-17 years</td>
<td>50.0-926.0 cells/mcL</td>
</tr>
<tr>
<td>Males</td>
<td>18-70 years</td>
<td>42.0-399.0 cells/mcL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference values have not been established for patients that are &lt;30 days of age.</td>
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</tbody>
</table>
Reference values have not been established for patients that are >70 years of age.

**Females**
- 1 month-17 years: 170.0-1,007.0 cells/mcL
- 18-70 years: 42.0-832.0 cells/mcL

Reference values have not been established for patients that are <30 days of age.
Reference values have not been established for patients that are >70 years of age.

**Clinical References:**

**CD43 Immunostain, Technical Component Only**

**Clinical Information:** CD43 (cluster of differentiation 43) is expressed by T lymphocytes and myeloid cells including granulocytes and precursors, monocytes, macrophages, histiocytes, plasma cells and megakaryocytes. In normal tonsil, CD43 will mainly show staining in T lymphocytes, histiocytes and plasma cells.

**Useful For:** Identification of T lymphocytes, monocytes, macrophages, granulocytes, plasma cells, and a subset of B lymphocytes

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CD45 Leukocyte Common Antigen (LCA) Immunostain, Technical Component Only**

**Clinical Information:** CD45 is also called leukocyte common antigen given its shared expression in the vast majority of cells of hematolymphoid lineage. The CD45 antibody used is a cocktail of 2 clones, PD7/26 (detects the CD45RB isoform), and 2B11 (detects a common CD45 protein). CD45 expression is very specific and quite sensitive for cells of hematolymphoid lineage, thus, distinguishing lymphoma/leukemia from other neoplasms. The main exception is classical Hodgkin lymphoma, in which CD45 expression is absent.

**Useful For:** Aiding in distinguishing lymphoma/leukemia from other neoplasms
**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD49d Cell Expression Evaluation, Varies**

**Clinical Information:** Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: - Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma - Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

**Useful For:** Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD49d Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

**Interpretation:** The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

**Reference Values:** Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.


**CD5 Immunostain, Technical Component Only**

**Clinical Information:** CD5 (cluster of differentiation 5) is expressed normally on all T cells (one of
the pan T-cell antigens). It can be aberrantly expressed by B-cell lymphomas (most commonly mantle cell
lymphoma, B-cell small lymphocytic lymphoma). Expression of CD5 is useful to support T-cell lineage in
T-cell lymphomas or to help subclassify B-cell lymphomas.

**Useful For:** Marker of T-cell lineage Phenotyping B-cell lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of
the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic
evaluation or second opinion of the case. The positive and negative controls are verified as showing
appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control
tissue is not included on the slide, a scanned image of the relevant quality control tissue is available
upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the
patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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CD52 Cell Expression Evaluation, Varies

**Clinical Information:** Monoclonal antibodies are critical tools for detecting cellular antigens in
various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg. CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

**Useful For:** Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD52 Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

**Interpretation:** The immunophenotyping report will summarize the pattern of antigenic expression
on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic
monoclonal antibody target.

**Reference Values:**
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the
corresponding cell-surface antigens in question.

**Clinical References:**
**CD56 Immunostain, Technical Component Only**

**Clinical Information:** CD56 is an adhesion molecule mediating homophilic and heterophilic adhesion in neurons, natural killer cells, and a small subset of CD4- and CD8-positive T cells. It is expressed in tumors with neuroendocrine differentiation (small cell lung carcinoma and neural-derived tumors) or natural killer cell lineage (subset of lymphomas). In normal small intestine, the ganglion cells in the muscle wall and nerves will show strong staining. Scattered lymphocytes may also be positive.

**Useful For:** Aiding in the identification of tumors with neuroendocrine differentiation Aiding in the identification of natural killer cell lineage in a subset of lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD57 Immunostain, Technical Component Only**

**Clinical Information:** CD57 (cluster of differentiation 57) is present in tumors of neuroectodermal origins; small cell lung carcinoma, carcinoid tumors, adenocarcinomas of the prostate. It is also expressed in normal and hyperplastic prostatic epitheliums as well as in natural killer (NK) cells and a subset of T cells.

**Useful For:** Marker of natural killer cells and a subset of follicular T helper cells Aiding in the identification of tumors of neuroectodermal origin

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**CD61 Immunostain, Technical Component Only**

**Clinical Information:** Cluster of differentiation 61 (CD61) shows cytoplasmic staining of normal and abnormal megakaryocytes and occasional endothelial cells. Antibodies to CD61 are most useful in recognizing micromegakaryocytes, cytologically abnormal megakaryocytes, and megakaryoblasts in cases of acute megakaryoblastic leukemia, myeloproliferative disorders, and myelodysplastic syndromes.

**Useful For:** Identification of micromegakaryocytes, cytologically abnormal megakaryocytes, and megakaryoblasts

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**CD68 (KP1) Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** In normal tissues, CD68 KP-1 stains the cytoplasm of the granulocytes and myeloid progenitors in the bone marrow, monocytes, and macrophages, and osteoclasts. KP-1 reacts against a carbohydrate moiety of CD68. Although CD68 KP-1 is primarily used as a histiocytic marker, it is not specific for histiocytes. It can also be expressed in malignant melanoma, granular cell tumors, peripheral nerve sheath tumors, malignant fibrous histiocytoma, and other mesenchymal neoplasms and rare carcinomas.

**Useful For:** Aiding in the identification of histiocytic and myeloid lineage cells

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

Clinical Information: In normal tissues, CD68 KP-1 stains the cytoplasm of the granulocytes and myeloid progenitors in the bone marrow, monocytes and macrophages, and osteoclasts. KP-1 reacts against a carbohydrate moiety of CD68. Although CD68 KP-1 is primarily used as a histiocytic marker, it is not specific for histiocytes. It can also be expressed in malignant melanoma, granular cell tumors, peripheral nerve sheath tumors, malignant fibrous histiocytoma, and other mesenchymal neoplasms, and rare carcinomas.

Useful For: Aids in the identification of histiocytic and myeloid lineage cells

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD68 (PG-M1) Immunostain, Technical Component Only

Clinical Information: In normal tissues, CD68 PG-M1 stains monocytes, macrophages and, to a lesser extent, neutrophils in a cytoplasmic granular staining pattern. It has greater specificity for monocytes and macrophages than does KP-1 but its immunohistochemical staining pattern in non-hematolymphoid tumors has not been studied as extensively as CD68 KP-1. Diagnostically, CD68 PG-M1 is usually applied to cases of acute leukemia to demonstrate monocytic differentiation and to cases of hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas.

Useful For: Identification of monocytic differentiation Phenotyping hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD7 Immunostain, Technical Component Only

Clinical Information: Cluster of differentiation 7 (CD7) is expressed normally on all T cells and...
natural killer cells. Expression of CD7 can be aberrantly lost in T-cell lymphomas, providing support for a diagnosis of T-cell lymphoma.

**Useful For:** Identification of T cells and natural killer cells

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CD71 Immunostain, Technical Component Only**

**Clinical Information:** The transferrin receptor, cluster of differentiation 71 (CD71), is highly expressed on the surface of cells of the erythroid lineage and mediates the uptake of transferrin-iron complexes. Transferrin receptor expression levels are highest in early erythroid precursors through the intermediate normoblast phase, expression then decreases through the reticulocyte phase.

**Useful For:** Assessment of erythroid lineage

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CD79a Immunostain, Technical Component Only**

**Clinical Information:** Cluster of differentiation 79a (CD79a) stains the cytoplasm and membrane of B lymphocytes and megakaryocytes. CD79a is a protein expressed on the surface of B lymphocytes at all stages of maturation, from B-lymphocyte precursors through plasma cells. Its function is to transduce the signal of antigen binding to immunoglobulin into the cytoplasm of the B lymphocyte initiating intracellular signaling. Antibodies to CD79a are diagnostically useful to demonstrate B-cell lineage of acute lymphoblastic leukemia, malignant lymphomas and chronic lymphoproliferative disorders.

**Useful For:** Phenotyping leukemias and lymphomas
**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CD8 Immunostain, Technical Component Only**

**Clinical Information:** Cluster of differentiation 8 (CD8) is expressed in a subset of T cells (cytotoxic T cells). Antibodies to CD8 are useful diagnostically to demonstrate cytotoxic T-lymphocyte lineage of lymphomas and chronic lymphoproliferative disorders.

**Useful For:** Identification of cytotoxic T cells

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CD8 T-Cell Immune Competence Panel, Global, Whole Blood**

**Clinical Information:** CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is one of the early cytokines produced by CD8 T cells; it is released within a few hours of activation.(1) The cytotoxic function is mediated by the contents of the cytolytic granules.(1) Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate.(2) CD8 T-cell activation occurs either through the T-cell receptor peptide major histocompatibility complex (MHC) or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of over-immunosuppression by therapeutic agents) results in reduced production of...
IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid-organ transplant recipients, to prevent graft-versus-host disease in allogeneic hematopoietic stem cell transplant patients, and to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of over-immunosuppression is a clinical challenge. Therapeutic drug monitoring is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. However, the levels of drugs measured in blood specimens do not directly correlate with the administered dose due to individual pharmacokinetic differences.(3) Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient's level of functional immune competence. This assay provides a means to evaluate over-immunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is increased to halt or prevent graft rejection, to provide information on a balance between over-immunosuppression with subsequent infectious comorbidities and under-immunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8.30 a.m. and noon with no change between noon and afternoon. Natural killer-cell counts, on the other hand, are constant throughout the day.(4) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(5-7) In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells.(5) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(8) and during summer compared to winter.(9) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Determining over immunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to over immunosuppression. IFN-gamma and CD107a and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

**Reference Values:** The appropriate age-related reference values will be provided on the report.

**CD8 T-Cell Immune Competence, Global, Blood**

**Clinical Information:** CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is one of the early cytokines produced by CD8 T cells; it is released within a few hours of activation.(1) The cytotoxic function is mediated by the contents of the cytolytic granules.(1) Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate.(2) CD8 T-cell activation occurs either through the T-cell receptor (TCR)-peptide-major histocompatibility complex (MHC) or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of overimmunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with overimmunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid organ transplant recipients, to prevent graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplant patients and to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of overimmunosuppression is a clinical challenge. Therapeutic drug monitoring (TDM) is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. But, the levels of drugs measured in blood do not directly correlate with the administered dose due to individual pharmacokinetic differences.(3) Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient’s level of functional immune competence. This assay provides a means to evaluate overimmunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is increased to halt or prevent graft rejection, to provide information on a balance between overimmunosuppression with subsequent infectious comorbidities and underimmunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. Natural Killer (NK) cell counts, on the other hand, are constant throughout the day.(4) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(5,6,7) In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells.(5) It is generally accepted that lower CD4 T cell counts are seen in the morning compared to the evening(8) and during summer compared to winter.(9) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Determining overimmunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to overimmunosuppression. IFN-gamma and CD107a and CD107b levels greater than the defined reference
range are unlikely to have any clinical significance.

**Reference Values:**
Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%

CD107a/b expression (as % CD8 T cells): 8.5-49.1%

Reference values have not been established for patients who are <19 years of age.

**Clinical References:**

**CD99 (MIC-2) Immunostain, Technical Component Only**

**Clinical Information:** Cluster of differentiation 99 (CD99) is the product of the MIC2 gene. It is expressed in normal tissues including some lymphocytes, pancreatic islet cells, granulosa cells of the ovary, Sertoli cells of the testis, and ependymal cells of the central nervous system. It is strongly expressed in Ewing sarcoma/primitive neuroectodermal tumor, distinguishing it from other small round blue cell tumors of childhood and adolescence.

**Useful For:** Identification of Ewing sarcoma and primitive neuroectodermal tumors

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CDH1 Gene, Full Gene Analysis, Varies**

**Clinical Information:** Hereditary diffuse gastric cancer (HDGC) is a rare autosomal dominant hereditary cancer syndrome associated with germline variants in the CDH1 gene, which encodes the
protein E-cadherin. HDGC is predominantly characterized by increased susceptibility to diffuse gastric cancer and lobular breast cancer. HDGC is highly penetrant since the risk for developing gastric cancer is 80% by age 80. Women also have an approximately 40% to 60% risk of breast cancer by age 80. Colorectal cancer has been reported in individuals with germline CDH1 variants, however, the specific lifetime risk for colorectal cancer is unknown. The International Gastric Cancer Linkage Consortium proposes clinical criteria for the selection of individuals who are at increased risk of having a germline CDH1 variant as follows: 1) two or more cases of diffuse gastric cancer (histopathological confirmation in at least 1 case) in first- or second-degree relatives in which at least 1 individual is diagnosed prior to age 50; 2) three or more documented cases of diffuse gastric cancer in first- or second-degree relatives regardless of age of onset; 3) individuals diagnosed with diffuse gastric cancer before the age of 40 regardless of family history; 4) personal or family history of diffuse gastric cancer and lobular breast cancer in first and second relatives with at least 1 diagnosis occurring before age 50.

Useful For: Confirmation of suspected clinical diagnosis of hereditary diffuse gastric cancer Identification of familial CDH1 variant to allow for predictive testing in family members Predictive testing of an asymptomatic child is not recommended.

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

Reference Values:
An interpretive report will be provided.


CDKN1C Gene, Full Gene Analysis, Varies

Clinical Information: The CDKN1C gene is an imprinted gene that has been associated with Beckwith-Wiedemann syndrome (BWS), intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies (IMAGe) syndrome, and Russell-Silver syndrome (RSS). Imprinting describes a difference in gene expression based on parent of origin. The majority of autosomal genes exhibit biallelic (maternal and paternal) expression, whereas imprinted genes are normally expressed from only one parent. CDKN1C is typically expressed on the maternally inherited allele. Â Beckwith-Wiedemann Syndrome: BWS is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroGLOSSIA, and hEMIHYPERTROPHIA. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Most cases of BWS are caused by hypomethylation of LIT1, paternal uniparental disomy of chromosome 11, or hypermethylation of H19. Approximately 5% to 10% of sporadic BWS cases and approximately 40% of BWS cases with a positive family history are caused by CDKN1C variants. The appropriate first-tier test in the evaluation of a possible diagnosis of BWS is BWRS / Beckwith-Wiedemann Syndrome/Russell-Silver Syndrome Molecular Analysis, Varies. This test may be considered when the results of BWS methylation analysis are negative, and there is still a strong clinical suspicion of BWS. Â Intrauterine Growth Restriction, Metaphyseal Dysplasia, Adrenal Hypoplasia Congenita, and Genital Anomalies Syndrome: Variants in
the CDKN1C gene have also been associated with IMAGe syndrome. The CDKN1C variants associated with IMAGe syndrome tend to be missense variants occurring in the PCNA-binding domain of the gene. Not every individual with a clinical diagnosis of IMAGe syndrome will have an identifiable CDKN1C variant. Russell-Silver Syndrome: RSS is a rare genetic condition with an incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth retardation with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include cafe au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia. RSS is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes: hypomethylation of IC1 (H19), maternal uniparental disomy (UPD) of chromosome 7, 11p15.5 duplications (rare), and chromosome 7 duplications (rare). CDKN1C variants have recently been identified as a cause of RSS in some families. This test may be considered when results of RSS methylation analysis and UPD 7 studies are negative and there is still a strong clinical suspicion of RSS.

**Useful For:**
- Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome following a normal result on methylation analysis
- Confirming a clinical diagnosis of intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies (IMAGe) syndrome
- Confirming a clinical diagnosis of Russell-Silver syndrome following a normal result on methylation analysis and uniparental disomy (UPD) 7 studies.

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CDX2 Immunostain, Technical Component Only**

**Clinical Information:** Caudal type homeobox 2 (CDX2) is a transcription factor belonging to the caudal type homeobox gene family. It is involved in regulating the proliferation and differentiation of intestinal epithelial cells.

**Useful For:** Identification of carcinoma of intestinal origin

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available.
upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CEBPA**

**CEBPA Mutations, Gene Sequencing, Varies**

**Clinical Information:** Acute myeloid leukemia (AML) with mutated CCAAT/enhancer-binding protein alpha (CEBPA) gene is a diagnostic category in the current WHO classification of hematopoietic neoplasms. In addition, CEBPA mutation on both alleles (so-called double mutation status) is considered a good prognostic feature in adults with newly diagnosed AML who have a normal karyotype or do not contain an alternate diagnostic genetic abnormality. Thus, evaluation for CEBPA mutations is necessary for accurate diagnosis in the current classification system and contributes prognostic information for a large group of AML patients.

**Useful For:** Initial evaluation of acute myeloid leukemia, both for assigning an appropriate diagnostic subclassification and as an aid for determining prognosis

**Interpretation:** The results will be given as positive or negative for CEBPA mutation and, if positive, the mutation will be described and single or double mutation status will be indicated.

**Reference Values:**
An interpretive report will be provided


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**FRCE**

**Cedar Red (Juniperus virginiana) IgE**

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

**Reference Values:**
<0.35 kU/L

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**CEDR**

**Cedar, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cedar
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: 
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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Reference values apply to all ages.


**Celery, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to celery
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: 
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>&gt; or =100</td>
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</tbody>
</table>

Reference values apply to all ages.


CELI 88906

Celiac Associated HLA-DQ Alpha 1 and DQ Beta 1 DNA Typing, Blood

Clinical Information: Celiac disease (gluten-sensitive enteropathy) is mediated by T lymphocytes in patients with genetic susceptibility. This genetic association is with certain HLA genes in the class II region (DQ alpha 1, DQ beta 1).

Useful For: Assessing risk of celiac disease

Interpretation: Most (90%-95%) patients with celiac disease have 1 or 2 copies of HLA-DQ2 haplotype (see below), while the remainder have HLA-DQ8 haplotype. Rare exceptions to these associations have been occasionally seen. In 1 study of celiac disease, only 0.7% of patients with celiac disease lacked the HLA alleles mentioned above. Results are reported as permissive, nonpermissive, or equivocal gene pairs. It is important to realize that these genes are also present in about 20% of people without celiac disease. Therefore, the mere presence of these genes does not prove the presence of celiac disease or that genetic susceptibility to celiac disease is present. The HLA-DQ molecule is composed of two chains: DQ alpha (encoded by HLA-DQA1 gene) and DQ beta (encoded by HLA-DQB1 gene). HLA-DQ typing can be performed by serological or molecular methods. Currently most laboratories perform typing by molecular methods. HLA-DQ2 and DQ8 as typed by serology are usually based on the molecular typing of the DQB1 chain only. The current molecular method allows typing for both the DQB1 and DQA1 chains and this has shown that there are different haplotypes of HLA-DQ2 and DQ8. Typing of these haplotypes is important in celiac disease as they carry different risk association. There are 2 common haplotypes of DQ2: 1. DQA1*05:01 with DQB1*02:01 also called DQ2.5 in celiac literature 2. DQA1*02:01 with DQB1*02:02 also called DQ2.2 in celiac literature A single haplotype (heterozygote) of DQ2.5 is permissive for presence of celiac genes. However, only a double haplotype (homozygous) of DQ2.2 is permissive for presence of celiac genes. There are few reports where a single haplotype of DQ2.2 is considered to be an equivocal risk. In some cases the DQ2.2 haplotype maybe present with a DQ7.5 haplotype (DQA1*05:05 with DQB1*03:01). In this case a DQ2.5 molecule can be formed by the combination of DQB1*02:02 from 1 chromosome and DQA1*05:05 from the other chromosome. These cases fall in the same category as the DQ2.5 heterozygote. There are 3 common haplotypes of DQ8: 1. DQA1*03:01 with DQB1*03:02 2. DQA1*03:02 with DQB1*03:02 3. DQA1*03:03 with DQB1*03:02 Any single haplotype (heterozygote) of DQ8 is permissive for celiac. Therefore, the gene pairs permissive for celiac are: 1. Heterozygote (single copy) -DQA1*05:XX with DQB1*02:01 -DQA1*05:XX with DQB1*02:02 -DQA1*03:XX with DQB1*03:02 2. Homozygous (2 copies) -DQA1*02:01 with DQB1*02:02 Gene pairs equivocal for celiac are 1. Heterozygote (single copy) -DQA1*02:01 with DQB1*02:02 2. Rare allele types of DQ2 and DQ8 other than those listed above all other gene pair combinations are considered non-permissive for celiac.
**Reference Values:**
An interpretive report will be provided.


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**Celiac Disease Comprehensive Cascade, Serum and Whole Blood**

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac Disease Comprehensive Cascade in Special Instructions. An individual suspected of having celiac disease may be HLA typed to determine if the individual has the susceptibility alleles DQ2 and/or DQ8. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA subtype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. This is typically accompanied by an improvement in clinical symptoms. It should be noted that HLA typing is not required to establish a diagnosis of celiac disease. Consider ordering CDSP / Celiac Disease Serology Cascade if HLA typing is not desired or has been previously performed.

**Useful For:** Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease) Comprehensive algorithmic evaluation including HLA typing

**Interpretation:** Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease. IgA-tTG, IgG-tTG, IgA-deamidated gliadin, and IgG-deamidated gliadin antibody assays are performed in this cascade. For individuals who have selective IgA deficiency with undetectable levels of IgA, only IgG-tTG and IgG-deamidated
gliadin antibody assays are performed. HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA DQ2 allele; most of the remaining patients with celiac disease have the HLA DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. Individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, should be referred for small intestinal biopsy. HLA typing may be especially helpful for those patients who have begun to follow a gluten-free diet prior to a confirmed diagnosis of celiac disease.(4) Tissue Transglutaminase (tTG) Antibody, IgA/IgG: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG isotype is performed. In these individuals, a positive IgG-tTG antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-tTG antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Antibody, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these individuals, a positive IgG-deamidated gliadin antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-deamidated gliadin antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial (EMA) Antibody, IgA: Positivity for EMA antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

Reference Values:
IMMUNOGLOBULIN A (IgA)
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

HLA-DQ TYPING
Presence of DQ2 or DQ8 alleles associated with celiac disease


Celiac Disease Gluten-Free Cascade, Serum and Whole Blood
Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy.(1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation.(2)
Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared with approximately 40% of the general population.(3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy.(1-3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient.(2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet.(1-3)

**Useful For:** Evaluating patients suspected of having celiac disease who are currently (or were recently) on a gluten-free diet

**Interpretation:** HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA-DQ2 allele; most of the remaining patients with celiac disease have the HLA-DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. For these individuals, no further serologic testing is required. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. For individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, small intestinal biopsy is recommended. Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable, but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease. Tissue Transglutaminase (tTG) Antibody, IgA/IgG: Individuals positive for tTG antibodies of the IgA and/or IgG isotype may have celiac disease and small intestinal biopsy is recommended. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Antibody, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA and/or IgG isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

**Reference Values:**

**HLA-DQ TYPING**

Presence of DQ2 or DQ8 alleles associated with celiac disease

Celiac Disease Serology Cascade, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type 1 diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared with approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet.

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for DQ2 and/or DQ8)

Interpretation: Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; IgA-tTG, IgG-tTG, IgA-deamidated gliadin, and IgG-deamidated gliadin antibody assays are performed in this cascade. For individuals who have selective IgA deficiency or undetectable levels of IgA, only IgG-tTG and IgG-deamidated gliadin antibody assays are performed. Tissue Transglutaminase (tTG) Ab, IgA/IgG: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for IgG antibodies of the IgG isotype is performed. In these individuals, a positive IgG-tTG antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-tTG antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Ab, IgA/IgG: Positivity forconstitutes a diagnosis of celiac disease. However, just as with the IgA-deamidated gliadin antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients.
patients who have been following a gluten-free diet. Endomysial (EMA) Ab, IgA: Positivity for EMA antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease as antibody levels decrease over time in patients who have been following a gluten-free diet.

**Reference Values:**

**Immunoglobulin A**
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL

**Clinical References:**
4. Update on celiac disease: New standards and new tests. 2008 Mayo Communique

**NCSPC 113338**

**Cell Concentration (Bill Only)**

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

**CCBF 8419**

**Cell Count and Differential, Body Fluid**

**Clinical Information:** Body fluids, other than the commonly analyzed urine and blood, include synovial, pleural, peritoneal, and pericardial fluids. These fluids may be present in increased volumes and may contain increased numbers of normal and abnormal cells in a variety of disease states.

**Useful For:** Aids in the diagnosis of joint disease, systemic disease, inflammation, malignancy, infection, and trauma, using body fluid specimens

**Interpretation:** Trauma and hemorrhage may result in increased red and white blood cells; RBCs predominate. WBCs are increased in inflammatory and infectious processes: -Neutrophils predominate in bacterial infections -Lymphocytes predominate in viral infections -Macrophages may be increased in inflammatory and infectious processes -Eosinophils may be increased in parasitic or fungal infections

**Reference Values:**
- **TOTAL NUCLEATED CELLS**
  - Synovial fluid: <150/mcL
  - Peritoneal/pleural/pericardial fluid: <500/mcL
- **NEUTROPHILS**
  - Synovial Fluid: <25%
  - Peritoneal/pleural/pericardial fluid: <25%
- **LYMPHOCYTES**
  - Synovial fluid: <75%
MONOCYTES/MACROPHAGES
Synovial fluid: < or = 70%


Cell-Free DNA BRAF V600, Blood

Clinical Information: This test uses DNA extracted from the peripheral blood to evaluate for the presence of BRAF V600E and V600K alterations. A positive result indicates the presence of an activating BRAF alteration and may be useful for guiding the treatment of individuals with melanoma. Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks.

Useful For: An alternative to invasive tissue biopsies for the determination of BRAF V600E and V600K alterations Identification of patients with melanoma who are most likely to benefit from targeted therapies This test is not intended for serial monitoring of patients with malignant melanoma, evaluating patients with other malignancies, or as a screening test to identify cancer.

Interpretation: An interpretive report will be provided.


Cell-Free DNA EGFR T790M Mutation Analysis, Blood

Clinical Information: EGFR-targeted tyrosine kinase inhibitors (eg, gefitinib and erlotinib) have been approved by the FDA for use in treating patients with non-small cell lung cancer (NSCLC) who previously failed to respond to traditional chemotherapy. However, the EGFR T790M mutation is associated with acquired resistance to tyrosine kinase inhibitor (TKI) therapy in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib. Recent data suggest that patients with metastatic NSCLC and the T790M mutation may benefit from osimertinib, an FDA-approved oral TKI that inhibits both EGFR-activating mutations and the T790M mutation.

Useful For: Determination of EGFR T790M mutation status in blood specimens as an alternative to invasive tissue biopsies Identification of patients with non-small cell lung cancer who harbor a T790M mutation and may benefit from specific EGFR-targeted therapies

Interpretation: An interpretive report will be provided.


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Cell-Free DNA KRAS 12, 13, 61, 146, Blood

Clinical Information: Approximately 30% to 50% of colorectal cancers (CRC) have mutations in KRAS. Most occur in hotspot regions in codons 12, 13, 61, and 146. These mutations lead to constitutive activation of the RAS/MAPK pathway downstream of epidermal growth factor receptor (EGFR), limiting the effectiveness of anti-EGFR therapies, such as cetuximab and panitumumab, which inhibit ligand-mediated activation of EGFR. Therefore, identification and quantitation of these mutations is critical in selecting the appropriate therapy. This test uses DNA extracted from peripheral blood to evaluate for the presence of KRAS (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutations. A positive result indicates the presence of an activating KRAS mutation and may be useful for guiding the treatment of individuals with colorectal cancer.

Useful For: As an alternative to invasive tissue biopsies for the determination of KRAS 12, 13, 61, 146 (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutation status. Selection of patients with colorectal cancer who are most likely to benefit from epidermal growth factor receptor (EGFR)-targeted therapies.

Interpretation: An interpretive report will be provided.

Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) syndrome variant of systemic sclerosis (scleroderma). CREST syndrome is characterized by the following clinical features: calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia. Centromere antibodies were originally detected by their distinctive pattern of fine-speckled nuclear staining on cell substrates used in the fluorescent antinuclear antibody test. In subsequent studies, centromere antibodies were found to react with several centromere proteins of 18 kDa, 80 kDa, and 140 kDa named as CENP-A, CENP-B, and CENP-C, respectively. Several putative epitopes associated with these autoantigens have been described. The CENP-B antigen is believed to be the primary autoantigen and is recognized by all sera that contain centromere antibodies.

**Useful For:** Evaluating patients with clinical signs and symptoms compatible with systemic sclerosis including skin involvement, Raynaud phenomenon, and arthralgias Aiding in the diagnosis of calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasis (CREST) syndrome

**Interpretation:** In various reported clinical studies, centromere antibodies occur in 50% to 96% of patients with calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasis (CREST) syndrome. A positive test for centromere antibodies is strongly associated with CREST syndrome. The presence of detectable levels of centromere antibodies may antedate the appearance of diagnostic clinical features of CREST syndrome by several years.

**Reference Values:**

- Class 1 or greater: (positive)
- <1.0 U (negative)

Reference values apply to all ages.

**Clinical References:**

## Cephalosporium acremonium, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to Cephalosporium acremonium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
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Reference values apply to all ages.


**CTSU 606147**

**Ceramide Trihexosides and Sulfatides, Random, Urine**

**Clinical Information:** Urinary excretion of ceramide trihexosides (CT) can be suggestive of Fabry disease, while excretion of sulfatide with or without CT can be suggestive of metachromatic leukodystrophy, multiple sulfatase deficiency, mucolipidosis II (I-cell disease), or saposin B deficiency. Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Affected individuals accumulate glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. Individuals with Fabry disease, regardless of the severity of symptoms, may show an increased excretion of CT in urine. Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder most commonly caused by a deficiency of the arylsulfatase A enzyme. Various sulfatides accumulate in the brain, nervous system, and visceral organs including the kidney and gallbladder and are excreted in the urine. Based on age of onset, the 3 clinical forms of MLD are late-infantile, juvenile, and adult, with late-infantile being the most common. All result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Symptoms may include hypotonia, clumsiness, diminished reflexes, slurred speech, behavioral problems, and personality changes. Individuals with MLD show an increased urinary excretion of sulfatides without CT. Saposin B deficiency is a rare cause of MLD with features that mimic MLD due to arylsulfatase A deficiency. However, individuals with saposin B deficiency have normal arylsulfatase A activity. Individuals with saposin B deficiency typically have an increased urinary excretion of both sulfatides and CT. Low arylsulfatase A activity has been found in some clinically normal parents and other relatives of MLD patients. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with a fairly common alternation in the arylsulfatase A gene (ARSA), which leads to low expression of the enzyme (5%-20% of normal). These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine sulfatides content is normal. Multiple sulfatase deficiency (MSD) is a rare autosomal recessive disorder caused by a defect in SUMF1, which is required for post-translational activation of the family of 17 sulfatase enzymes, including arylsulfatase A and B. The clinical features of MSD resemble those of late-infantile MLD. Dysmorphic features similar to the mucopolysaccharidoses and ichthyosis as seen in steroid sulfatase deficiency are also common. Individuals with MSD typically have an increased urinary excretion of sulfatides as well as increased urinary glycosaminoglycans (test ID: MPSSC / Mucopolysaccharides Screen, Random, Urine). Mucolipidosis II, also known as I-cell disease, is a rare autosomal recessive disorder with features of both mucopolysaccharidoses and
sphingolipidoses. I-cell disease is a progressive disorder characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. Individuals with I-cell disease have abnormal oligosaccharide profiles (test ID: OLIGU / Oligosaccharide Screen, Random, Urine) and may show an increased urinary excretion of both CT and sulfatides.

**Useful For:** Identifying patients with Fabry disease Identifying patients with metachromatic leukodystrophy Identifying patients with saposin B deficiency Identifying patients with multiple sulfatase deficiency Identifying patients with mucolipidosis II (I-cell disease)

**Interpretation:** The pattern of ceramide trihexosides or sulfatide excretion will be described. A normal pattern of excretion suggests absence of these diseases (see Cautions). Evidence of ceramide trihexoside accumulation suggests decreased or deficient alpha-galactosidase activity. See Fabry Disease Testing Algorithm in Special Instructions. Evidence of sulfatide accumulation suggests decreased or deficient arylsulfatase A activity. Follow-up with the specific enzyme assay is recommended: -ARSAW / Arylsulfatase A, Leukocytes -ARSU / Arylsulfatase A, 24 Hour, Urine To exclude multiple sulfatase deficiency (MSD), determination of I2SW / Iduronate-2-Sulfatase, Whole Blood (or I2SBS / Iduronate-2-Sulfatase, Blood Spot) is recommended. Evidence of both ceramide trihexoside and sulfatide accumulation suggests a diagnosis of mucolipidosis II (I-cell disease) or saposin B deficiency. Follow-up testing to rule-out I-cell disease may include molecular analysis of the GNPTAB gene or measurement of serum hydrolases (test ID: NAGS / Hexosaminidase A and Total Hexosaminidase, Serum) Molecular genetic testing is required to confirm saposin B deficiency. See Lysosomal Storage Disorders Diagnostic Algorithm, Part 2 in Special Instructions

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

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**Cerebrospinal Fluid (CSF) IgG Index Profile, Serum and Spinal Fluid**

**Clinical Information:** Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) such as multiple sclerosis (MS), neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis may be due to local (intrathecal) synthesis of IgG. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.

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SFIG 610783

Cerebrospinal Fluid (CSF) IgG Index Profile, Serum and Spinal Fluid

Clinical Information: Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) such as multiple sclerosis (MS), neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis may be due to local (intrathecal) synthesis of IgG. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.
Useful For: Aiding in the diagnosis of multiple sclerosis and other central nervous system inflammatory conditions

Interpretation: Cerebrospinal fluid (CSF) IgG synthesis rate indicates the rate of increase in the daily CSF production of IgG in milligrams per day. A result greater than 12 mg/24h is elevated. A CSF index greater than 0.85 is elevated and indicative of increased synthesis of IgG.

Reference Values:
CSF index: 0.00-0.85
  CSF IgG: 0.0-8.1 mg/dL
  CSF albumin: 0.0-27.0 mg/dL
  Serum IgG
  0-4 months: 100-334 mg/dL
  5-8 months: 164-588 mg/dL
  9-14 months: 246-904 mg/dL
  15-23 months: 313-1,170 mg/dL
  2-3 years: 295-1,156 mg/dL
  4-6 years: 386-1,470 mg/dL
  7-9 years: 462-1,682 mg/dL
  10-12 years: 503-1,719 mg/dL
  13-15 years: 509-1,580 mg/dL
  16-17 years: 487-1,327 mg/dL
  > or =18 years: 767-1,590 mg/dL
  Serum albumin
  > or =12 months: 3,500-5,000 mg/dL
  Reference values have not been established for patients who are <12 months of age.
  CSF IgG/albumin: 0.00-0.21
  Serum IgG/albumin: 0.0-0.4
  CSF IgG synthesis rate: 0-12 mg/24 hours


Cerebrospinal Fluid (CSF) IgG Index, Spinal Fluid

Clinical Information: Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) such as multiple sclerosis (MS), neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis may be due to local (intrathecal) synthesis of IgG. Elevations of CSF IgG or the CSF/serum IgG ratio may also occur as a result of permeability of the blood brain barrier, and hence, a correction using albumin measurements in CSF and serum is appropriate. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.
Useful For: Aids in the diagnosis of multiple sclerosis and other central nervous system inflammatory conditions

Interpretation: Cerebrospinal fluid (CSF) IgG synthesis rate indicates the rate of increase in the daily CSF production of IgG in milligrams per day. A result greater than 12 mg/24 hours is elevated. A CSF index greater than 0.85 is elevated and indicative of increased synthesis of IgG.

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

CSF index: 0.00-0.85
CSF IgG: 0.0-8.1 mg/dL
CSF albumin: 0.0-27.0 mg/dL
CSF IgG/albumin: 0.00-0.21
CSF IgG synthesis rate: 0-12 mg/24 hours

Clinical References:

Cerebrotendinous Xanthomatosis, Blood

Clinical Information: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of bile acid synthesis resulting from the deficiency of the mitochondrial enzyme, sterol 27-hydrolase. Sterol 27-hydrolase facilitates the first step of sterol degradation in the formation of bile acids; consequently patients with CTX will experience increased storage of the sterol, cholestenol, and ketosterol bile acid precursors (7-alpha-hydroxy-4-cholesten-3-one [7a-C4] and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one [7a12aC4]) in multiple tissues throughout the body with a resulting deficiency of the bile acid, chenodeoxycholic acid (CDCA). CTX is caused by variants in the CYP27A1 gene. Patients with CTX can present with a constellation of findings including infantile onset diarrhea, childhood onset cataracts, development of tendon/cerebral xanthomas in adolescence and early adulthood, early onset osteoporosis, as well as a broad array of neuropsychological manifestations such as intellectual disability, dementia, psychiatric symptoms, ataxia, pyramidal signs, dystonia, and muscle weakness. Patients may occasionally present with cholestatic liver disease, which may present as jaundice, poor growth, and hepatosplenomegaly. Intrafamilial variability exists, and some heterozygous carriers may experience a higher incidence of cardiac disorders or gallstones. Treatment with CDCA normalizes bile acid synthesis and suppresses cholestenol biosynthesis, with improvement of clinical symptoms and arrest of disease progression. Supplementation with beta-hydroxy beta-methylglutaryl-CoA (HMG-CoA) inhibitors and coenzyme Q10 has been proposed. The availability of effective therapy makes early diagnosis and treatment of patients with CTX essential. The estimated incidence of CTX is 1 in 50,000 individuals of Northern European ancestry and as high as 1 in 440 in the Druze population of Israel. The diagnostic evaluation of patients with suspected CTX may reveal abnormalities on brain magnetic resonance imaging (such as cerebellar atrophy, decrease in volume of grey and white matter, and abnormal white matter signal) in addition to the biochemical and clinical abnormalities. The biochemical diagnosis of CTX can be confirmed by molecular genetic analysis of the CYP27A1 gene (included in: NPPAN / Peripheral Neuropathy Genetic Panels by Next-Generation Sequencing [NGS], Blood).

Useful For: Evaluating patients with a clinical suspicion of cerebrotendinous xanthomatosis (CTX)
CTXBS
65630
Cerebrotendinous Xanthomatosis, Blood Spot

Clinical Information: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of bile acid synthesis resulting from the deficiency of the mitochondrial enzyme, sterol 27-hydroxylase. Sterol 27-hydroxylase facilitates the first step of sterol degradation in the formation of bile acids; consequently patients with CTX will experience increased storage of the sterol, cholestenol, and ketosterol bile acid precursors (7-alpha-hydroxy-4-cholesten-3-one [7a-C4] and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one [7a12aC4]) in multiple tissues throughout the body with a resulting deficiency of the bile acid, chenodeoxycholic acid (CDCA). CTX is caused by variants in the CYP27A1 gene. Patients with CTX can present with a constellation of findings including infantile onset diarrhea, childhood onset cataracts, development of tendon/cerebral xanthomas in adolescence and early adulthood, early onset osteoporosis, as well as a broad array of neuropsychological manifestations such as intellectual disability, dementia, psychiatric symptoms, ataxia, pyramidal signs, dystonia, and muscle weakness. Patients may occasionally present with cholestatic liver disease, which may present as jaundice, poor growth, and hepatosplenomegaly. Intrafamilial variability exists and some heterozygous carriers may experience a higher incidence of cardiac disorders or gallstones. Treatment with chenodeoxycholic acid (CDCA) normalizes bile acid synthesis and suppresses cholestenol biosynthesis, with improvement of clinical symptoms and arrest of disease progression. Supplementation with beta-hydroxy beta-methylglutaryl-CoA (HMG-CoA) inhibitors and coenzyme Q10 has been proposed. The availability of effective therapy makes early diagnosis and treatment of patients with CTX essential. The estimated incidence of CTX is 1 in 50,000 individuals of Northern European ancestry and as high as 1 in 440 in the Druze population of Israel. The diagnostic evaluation of patients with suspected CTX may reveal abnormalities on brain magnetic resonance imaging (such as cerebellar atrophy, decrease in volume of grey and white matter, and abnormal white matter signal) in addition to the biochemical and clinical abnormalities. The biochemical diagnosis of CTX can be confirmed by molecular genetic analysis of the CYP27A1 gene (included in: NPPAN / Peripheral Neuropathy Genetic Panels by Next-Generation Sequencing [NGS], Blood).

Useful For: Evaluating patients with a clinical suspicion of cerebrotendinous xanthomatosis (CTX) using dried blood spot specimens Monitoring individuals with CTX on chenodeoxycholic acid (CDCA) therapy This test is not useful for the identification of carriers This test is not useful for the evaluation of bile acid malabsorption

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7a-C4) and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4) is strongly suggestive of cerebrotendinous xanthomatosis.
alpha-dihydroxycholesterol-4-en-3-one (7a12aC4) is strongly suggestive of cerebrotendinous xanthomatosis (CTX).

**Reference Values:**

7-ALPHA-HYDROXY-4-CHOLESTEN-3-ONE (7a-C4)

Cutoff: ≤ or =0.750 nmol/mL

7-ALPHA,12-ALPHA-DIHYDROXYCHOLEST-4-en-3-ONE (7a12aC4)

Cutoff: ≤ or =0.250 nmol/mL

**Clinical References:**


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**CTXP 65631**

**Cerebrotendinous Xanthomatosis, Plasma**

**Clinical Information:** Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of bile acid synthesis resulting from the deficiency of the mitochondrial enzyme, sterol 27-hydrolase. Sterol 27-hydrolase facilitates the first step of sterol degradation in the formation of bile acids; consequently patients with CTX will experience increased storage of the sterol, cholestenol, and ketosterol bile acid precursors (7-alpha-hydroxy-4-cholesten-3-one [7a-C4] and 7-alpha,12-alpha-dihydroxycholester-4-en-3-one [7a12aC4]) in multiple tissues throughout the body with a resulting deficiency of the bile acid, chenodeoxycholic acid (CDCA). CTX is caused by variants in the CYP27A1 gene. Patients with CTX can present with a constellation of findings including infantile onset diarrhea, childhood onset cataracts, development of tendon/cerebral xanthomas in adolescence and early adulthood, early onset osteoporosis, as well as a broad array of neuropsychological manifestations such as intellectual disability, dementia, psychiatric symptoms, ataxia, pyramidal signs, dystonia, and muscle weakness. Patients may occasionally present with cholestatic liver disease, which may present as jaundice, poor growth, and hepatosplenomegaly. Intrafamilial variability exists and some heterozygous carriers may experience a higher incidence of cardiac disorders or gallstones. Treatment with CDCA normalizes bile acid synthesis and suppresses cholestenol biosynthesis, with improvement of clinical symptoms and arrest of disease progression. Supplementation with beta-hydroxy beta-methylglutaryl-CoA (HMG-CoA) inhibitors and coenzyme Q10 has been proposed. The availability of effective therapy makes early diagnosis and treatment of patients with CTX essential. The estimated incidence of CTX is 1 in 50,000 individuals of Northern European ancestry and as high as 1 in 440 in the Druze population of Israel. The diagnostic evaluation of patients with suspected CTX may reveal abnormalities on brain magnetic resonance imaging (such as cerebellar atrophy, decrease in volume of grey and white matter, and abnormal white matter signal) in addition to the biochemical and clinical abnormalities. The biochemical diagnosis of CTX can be confirmed by molecular genetic analysis of the CYP27A1 gene (included in: NPPAN / Peripheral Neuropathy Genetic Panels, Next-Generation Sequencing (NGS), Blood).

**Useful For:** Evaluating patients with a clinical suspicion of cerebrotendinous xanthomatosis (CTX) using plasma specimens Monitoring of individuals with CTX on chenodeoxycholic acid (CDCA) therapy This test is not useful for the identification of carriers This test is not useful for the evaluation of bile acid malabsorption

**Interpretation:** An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7a-C4) and 7-alpha,12-alpha-dihydroxycholesterol-4-en-3-one (7a12aC4) is strongly suggestive of cerebrotendinous xanthomatosis.

**Reference Values:**
7-ALPHA-HYDROXY-4-CHOLESTEN-3-ONE (7a-C4)
Cutoff: < or =0.300 nmol/mL

7-ALPHA,12 ALPHAI2 C4 DIHYDROXYCHOLEST-4-en-3-ONE (7a12aC4)
Cutoff: < or =0.100 nmol/mL


Certolizumab and Anti-Certolizumab Antibody, DoseASSURE CTZ

Useful For: Provides certolizumab drug concentration and anti-certolizumab antibodies in order to optimize treatment and facilitate clinical decision-making. This assay may be helpful in any patient on certolizumab therapy for Crohn's disease, psoriasis, or other autoimmune condition.

Reference Values:
Certolizumab:
Quantitation Limit: <1.0 ug/mL
Results of 1 ug/mL or higher indicate detection of certolizumab

Anti-Certolizumab Antibody:
Quantitation Limit: <40 ng/mL
Results of 40 ng/mL or higher indicate detection of anti-certolizumab pegol antibodies.

Ceruloplasmin, Serum

Clinical Information: Ceruloplasmin is a positive acute-phase reactant and a copper-binding protein that accounts for over 95% of serum copper in normal adults. Ceruloplasmin is measured primarily to assist with a diagnosis of Wilson disease. Other indications include Menkes disease, dietary copper insufficiency, and risk of cardiovascular disease. Wilson disease is a rare inherited disorder of copper transport that results in low serum copper and ceruloplasmin and accumulation of copper in various tissues. The pathological accumulation of copper in the liver, brain, cornea, and kidney causes cirrhosis, neuropsychiatric symptoms, Kayser-Fleischer rings, and hematuria/proteinuria, respectively. See Wilson Disease Testing Algorithm in Special Instructions for appropriate use of clinical findings, serum biomarkers, genetic tests, and tissue biopsies when working up suspected cases. Menkes disease is an X-linked disorder in which dietary copper is absorbed from the gastrointestinal tract but cannot be transported, so copper is not available to the liver for incorporation into ceruloplasmin. Dietary ceruloplasmin deficiency may be due to inadequate dietary copper intake, long-term parenteral nutrition without copper supplementation, malabsorption, penicillamine therapy, or a combination of these.

Useful For: Investigation of patients with possible Wilson disease

Interpretation: Low concentrations of ceruloplasmin are consistent with Wilson disease and warrant further investigation. Values vary considerably from patient to patient and may be in the normal range in some patients with Wilson disease (indicating a different primary defect). Ceruloplasmin is a positive acute-phase reactant. Increases in serum ceruloplasmin have been reported during pregnancy, in women...
taking oral contraceptives, in hepatitis, pneumonia, tuberculosis, rheumatoid arthritis, myocardial infarction, various forms of anemia, and many obscure neurological disorders.

**Reference Values:**

**Males:**
- 0-8 weeks: 7.4-23.7 mg/dL
- 9 weeks-5 months: 13.5-32.9 mg/dL
- 6-11 months: 13.7-38.9 mg/dL
- 12 months-7 years: 21.7-43.3 mg/dL
- 8-13 years: 20.5-40.2 mg/dL
- > or =18 years: 19.0-31.0 mg/dL

**Females:**
- 0-8 weeks: 7.4-23.7 mg/dL
- 9 weeks-5 months: 13.5-32.9 mg/dL
- 6-11 months: 13.7-38.9 mg/dL
- 12 months-7 years: 21.7-43.3 mg/dL
- 8-13 years: 20.5-40.2 mg/dL
- > or =18 years: 20.0-51.0 mg/dL

**Clinical References:**

**CFTR Gene, Full Gene Analysis, Varies**

**Clinical Information:** Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. Clinical diagnosis is generally made based on these features, combined with a positive sweat chloride test or positive nasal potential difference. CF can also have an atypical presentation and may manifest as congenital bilateral absence of the vas deferens (CBAVD), chronic idiopathic pancreatitis, bronchiectasis, or chronic rhinosinusitis. Several states have implemented newborn screening for CF, which identifies potentially affected individuals by measuring immunoreactive trypsinogen in a dried blood specimen collected on filter paper. If a clinical diagnosis of CF has been made, molecular testing for common CF mutations is available. To date, over 1,500 mutations have been described within the CF gene, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, deltaF508, accounts for approximately 67% of the mutations worldwide and approximately 70% to 75% in the North American Caucasian population. Most of the remaining mutations are rather rare, although some show a relatively higher prevalence in certain ethnic groups or in some atypical presentations of CF, such as isolated CBAVD. The recommended approach for confirming a CF diagnosis or detecting carrier status begins with molecular tests for the common CF mutations (eg, CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel, Varies). This test, CFTR Gene, Full Gene Analysis, Varies may be ordered if 1 or both disease-causing mutations are not detected by the targeted mutation analysis. Full gene analysis, through sequencing and dosage analysis of the CFTR gene, is utilized to detect private mutations. Together, full gene analysis of the CFTR gene and deletion/duplication analysis identify over 98% of the sequence variants in the coding region and splice junctions. Of note, FDA guidance has indicated that CFTR potentiator or combination chemical chaperone/potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least 1 copy of a small subset of mutations. If one of the mutations associated with an FDA-approved therapy is identified, this information will be included in the interpretive report. See Cystic Fibrosis Molecular Diagnostic Testing.
Algorithm in Special Instructions for additional information.

**Useful For:** Follow-up testing to identify mutations in individuals with a clinical diagnosis of cystic fibrosis (CF) and a negative targeted mutation analysis for the common mutations. Identification of mutations in individuals with atypical presentations of CF (e.g., congenital bilateral absence of the vas deferens or pancreatitis). Identification of mutations in individuals where detection rates by targeted mutation analysis are low or unknown for their ethnic background. Identification of patients who may respond to cystic fibrosis transmembrane conductance regulator (CFTR) potentiator therapy. This is not the preferred genetic test for carrier screening or initial diagnosis. For these situations, order CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel, Varies

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CGO Custom Gene Panel (LPGD) (Bill Only)**

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

**Chaetomium globosum, IgE, Serum**

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


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**FAMCE**

**Cheese American IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Ä̈<a–c 0.69 Low Positive 2 0.70 Ä̈<a–c 3.49 Moderate Positive 3 3.50 Ä̈<a–c 17.49 Positive 4 17.50 Ä̈<a–c 49.99 Strong Positive 5 50.00 Ä̈<a–c 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**FCCGG**

**Cheese Cheddar IgG**

**Interpretation:**

**Reference Values:**

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

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**FSCE**

**Cheese Swiss IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Ä̈<a–c 0.69 Low Positive 2 0.70 Ä̈<a–c 3.49 Moderate Positive 3 3.50 Ä̈<a–c 17.49 Positive 4 17.50 Ä̈<a–c 49.99 Strong Positive 5 50.00 Ä̈<a–c 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT     800-533-1710 or 507-266-5700 or mayocliniclabs.com
Cheese, Cheddar, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to cheddar cheese Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Cheese, Mold, IgE, Serum

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

**Useful For:** May be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. May be useful to identify allergens that may be responsible for allergic disease or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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

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<tr>
<td>4</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Cherry, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cherry. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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

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<tr>
<td>6</td>
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<td>Strongly positive Reference values</td>
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</tbody>
</table>

apply to all ages.


CTRE 82607

Chestnut Tree, IgE, Serum

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

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

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

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Chestnut, Sweet, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to sweet chestnut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

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

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
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Clinical Information: Imatinib mesylate, a small molecule tyrosine kinase inhibitor from the 2-phenylaminopyrimidine class of compounds, has shown activity in the treatment of malignancies that are associated with the constitutive activation of a specific subgroup of tyrosine kinases. A novel tyrosine kinase, generated from fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRA gene, was identified in 9 of 16 patients (56%) with hypereosinophilic syndrome (HES). This fusion results from an approximate 800 kb interstitial chromosomal deletion that includes the cysteine-rich hydrophobic domain 2 (CHIC2) locus at 4q12. FIP1L1-PDGFRA is a constitutively activated tyrosine kinase that transforms hematopoietic cells, and is a therapeutic target for imatinib in a subset of HES patients. Mast cell disease (MCD) is a clinically heterogeneous disorder wherein accumulation of mast cells (MC) may be limited to the skin (cutaneous mastocytosis) or involve 1 or more extra-cutaneous organs (systemic MCD [SMCD]). SMCD is often associated with eosinophilia (SMCD-eos). We recently tested the therapeutic activity of imatinib in 12 adults with SMCD-eos. In this study, we demonstrated that FIP1L1-PDGFRA is the therapeutic target of imatinib in the specific subset of patients with SMCD-eos. Furthermore, we provided evidence that the CHIC2 deletion is a surrogate marker for the FIP1L1-PDGFRA fusion.

Useful For: Providing genetic information for patients with hypereosinophilic syndrome (HES) and systemic mast cell disease (SMCD) involving CHIC2 deletion Identifying and tracking chromosome abnormalities and response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range. Detection of an abnormal clone is usually associated with hypereosinophilic syndrome or systemic mastocytosis associated with eosinophilia. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.


Chick Pea, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to chick pea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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Reference values apply to all ages.


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**CDROP 82142**

**Chicken Droppings, IgE, Serum**

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

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

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

**Reference Values:**

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Reference values apply to all ages.

### Clinical References:

FCHXG
57625

Chicken IgG

Interpretation:

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

CSPR
82351

Chicken Serum Proteins, IgE, Serum

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

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

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

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</tr>
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</table>

Reference values apply to all ages.

**Chicken, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to chicken Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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Reference values apply to all ages.


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**Chikungunya IgG, Antibody, Serum**

**Reference Values:** Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

**Chikungunya IgM and IgG, Antibody, Serum**
**Clinical Information**: Chikungunya virus (ChikV) is a single-stranded RNA alphavirus and a member of the Togaviridae family of viruses. The name Chikungunya is derived from the language of the Makonde ethnic groups in southeast Africa and means "that which bends" or "stooped walk." This is in reference to the hunched-over appearance of infected individuals due to the characteristically painful and incapacitating arthralgia caused by the virus. ChikV is endemic throughout Africa, India, and more recently the Caribbean islands. In 2014, the first case of autochthonous or local transmission in the United States occurred in Florida. Humans are the primary reservoir for ChikV and Aedes species mosquitoes are the primary vectors for transmission. Unlike other mosquito-borne viruses such as West Nile virus (WNV) and Dengue, the majority of individuals who are exposed to ChikV become symptomatic, with the most severe manifestations observed at the extremes of age and in those with suppressed immunity. Once exposed to ChikV, individuals develop lasting immunity and protection from reinfection. Prior to development of symptoms, the incubation period ranges, on average, from 3 to 7 days. Infected patients typically present with sudden onset high fever, incapacitating joint pain, and often a maculopapular rash lasting anywhere from 3 to 10 days. Notably, symptom relapse can occur in some individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

**Useful For**: Aiding in the diagnosis of recent infection with Chikungunya virus in patients with recent travel to endemic areas and a compatible clinical syndrome

**Interpretation**: IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists.
IgM and IgG Positive: -IgM and IgG antibodies to Chikungunya virus detected, suggesting recent or past infection. IgM antibodies to Chikungunya virus may remain detectable for 3 to 4 months post-infection. IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection.
Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection. IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

**Reference Values**:
IgM: Negative
IgG: Negative
Reference values apply to all ages.

**Clinical References**: Pan American Health Organization. Preparedness and Response for Chikungunya virus. Introduction into the Americas. PAHO 2011
fever and joint pain. There is no specific antiviral treatment for chikungunya virus infection. Most cases of disease have occurred in Africa, Asia, Europe, and the Indian and Pacific Oceans, but transmission of CHIK has been identified in Caribbean countries and South American regions, as well as foci in the southern United States. Infection with chikungunya virus may be suspected based on symptoms (fever, joint pain, and headache) and recent history of travel. A diagnosis of CHIK infection can be confirmed through laboratory tests on serum or cerebrospinal fluid. This assay is designed to detect only species of clinical significance and is to be used for patients with a clinical history and symptoms consistent with chikungunya infection.

Useful For: Qualitative detection of chikungunya virus in serum after early symptom onset (ideally <7 days) This test is not recommended for screening healthy patients.

Interpretation: A positive test result indicates the presence of chikungunya virus RNA in the specimen. A negative test result with a positive internal control indicates that chikungunya virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of PCR inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:
Negative

**Chili Pepper, IgE, Serum**

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

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

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

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<td>3.50-17.4</td>
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<tr>
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<td>&gt; or =100</td>
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</table>

recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. Polymerase chain reaction is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

**Interpretation:** An interpretive report will be provided, which defines unique features of the donor's cells. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CHIMS 62984**

**Chimerism Transplant Sorted Cells, Varies**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. Polymerase chain reaction is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen in sorted cell fractions An indicator of bone marrow transplant success

**Interpretation:** An interpretive report will be provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell
analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Chimerism-Donor, Varies**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen. This test evaluates the donor specimen prior to the recipient bone marrow transplant.

**Useful For:**
- Evaluating the donor cells prior to bone marrow transplant
- Determining the relative amounts of donor and recipient cells in a specimen. An indicator of bone marrow transplant success

**Interpretation:**
An interpretive report will be provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
CHRGB 83186

**Chimerism-Recipient Germline (Pretransplant), Varies**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor’s and the recipient’s DNA prior to transplantation and then examining the recipient’s blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen. This test evaluates the recipient specimen prior to bone marrow transplant.

**Useful For:** Evaluating the recipient cells prior to bone marrow transplant

**Interpretation:** An interpretive report will be provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

SCLAM 8142

**Chlamydia Serology, Serum**

**Clinical Information:** Members of the family Chlamydiaceae are small, nonmotile, gram-negative, obligate intracellular organisms that grow in the cytoplasm of host cells. Two genera of clinical importance are Chlamydia, which includes Chlamydia trachomatis, and Chlamydophila, which includes Chlamydophila pneumoniae and Chlamydophila psittaci. These organisms share many features of bacteria and are susceptible to antibiotic therapy. They are also similar to viruses, requiring living cells for multiplication. The chlamydial life cycle can be divided into 2 distinct phases: an extracellular, nonreplicating, infectious stage and an obligate intracellular, replicating, noninfectious stage. The
infectious form, or elementary body (EB), attaches to the target cell membrane and enters the cell via a phagosome. After cell entry, the EB reorganizes into reticulate particles (forming inclusion bodies) and binary fission begins. After 18 to 24 hours, reticulate particles condense to form EBs. These new EBs are released, beginning another infection cycle. C psittaci is the causative agent of psittacosis, a disease characterized by pneumonia, headache, altered mentation, and hepatosplenomegaly. Psittacosis is acquired by airborne transmission from infected birds. C pneumoniae (formerly known as Taiwan acute respiratory agent: TWAR and, more recently, as Chlamydia pneumoniae) causes pneumonia in humans. It is unique because it is a primary pathogen of humans, is spread from human to human, and apparently has no animal or bird host. Chlamydothilia pneumoniae is responsible for approximately 10% of pneumonia cases. C trachomatis has been implicated in a wide variety of infections in humans. It is a common cause of nongonococcal urethritis and cervicitis, and many systemic complications of chlamydial infections have been described. In females, this organism is a cause of pelvic inflammatory disease, salpingitis, and endometritis. In males, epididymitis and Reiter syndrome occur. Lymphogranuloma venereum is a sexually transmitted infection caused by C trachomatis. It presents with a transient primary genital lesion followed by suppurative regional lymphadenopathy. Occasionally, severe proctitis or proctocolitis may develop. C trachomatis also causes ophthalmologic infections, such as trachoma (rare in the United States), adult inclusion conjunctivitis and inclusion conjunctivitis in neonates. These disorders have traditionally been diagnosed by cytologic detection or culture. However, molecular detection methods (CTRNA / Chlamydia trachomatis by Nucleic Acid Amplification [HOLOGIC], Varies) may now represent a more sensitive diagnostic approach.

Fitz-Hugh-Curtis syndrome (perihepatitis) has been associated with chlamydiae.

Useful For: Aiding in the clinical diagnosis of chlamydial infections This test is not intended for medical-legal use.

**Interpretation:**
- **IgG:** Chlamydothilia pneumoniae > or =1:512 IgG endpoint titers of 1:512 or more are considered presumptive evidence of current infection. <1:512 and > or =1:64 A single specimen endpoint titer ofÂ from 1:64 to 1:512 should be considered evidence of infection at an undetermined time. A second specimen drawn 10 to 21 days after the original draw should be tested in parallel with the first. If the second specimen exhibits a titer 1:512 or more or a 4-fold increase over that of the initial specimen, current (acute) infection is indicated. Unchanging titers from 1:64 to 1:512 suggest past infection. <1:64 IgG endpoint titers below 1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. Chlamydothilia pneumoniae antibody is detectable in 25% to 45% of adults tested. Chlamydothilia psittaci and Chlamydia trachomatis > or =1:64 IgG endpoint titers of 1:64 or more are considered presumptive evidence of current infection. <1:64 IgG endpoint titers below 1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. IgM Chlamydothilia pneumoniae, Chlamydothilia psittaci, and Chlamydia trachomatis > or =1:10 IgM endpoint titers of 1:10 or more are considered presumptive evidence of infection. <1:10 IgM endpoint titers below 1:10 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels.

**Reference Values:**
- **Chlamydothilia pneumoniae**
  - IgG: <1:64
  - IgM: <1:10

- **Chlamydothilia psittaci**
  - IgG: <1:64
  - IgM: <1:10

- **Chlamydia trachomatis**
  - IgG: <1:64
  - IgM: <1:10

**Clinical References:**
1. Movahed MR: Infection with Chlamydia pneumoniae and atherosclerosis: a
Chlamydia trachomatis and Neisseria gonorrhoeae, Miscellaneous Sites, Nucleic Acid Amplification, Varies

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection in the United States.(1,2) In 2010, 1.3 million documented cases were reported to the CDC.(2) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile.(2) Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C. trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection.(2) Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure.(2) Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common sexually transmitted infection (STI), with 301,174 cases of gonorrhea reported to CDC in 2009.(2,3) Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence).(2,3) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance.(2) Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections.(2) However, organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(4-6) Immunoassays and non-amplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT.(2) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases of both chlamydia and gonorrhea.(2-6) Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to
seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis and Neisseria gonorrhoeae in non-FDA-approved specimen types This test is not intended for use in medico-legal applications. This test is not useful for the detection of Chlamydia pneumoniae.

**Interpretation:** A positive result indicates that rRNA of Chlamydia trachomatis and/or Neisseria gonorrhoeae is present in the specimen tested and strongly supports a diagnosis of chlamydial/gonorrheal infection. A negative result indicates that rRNA for C trachomatis and/or N gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient’s clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N gonorrhoeae), if appropriate. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of indeterminate indicates that a new specimen should be collected. This test has not been shown to cross react with commensal (nonpathogenic) Neisseria species present in the oropharynx.

**Reference Values:**
Negative

**Clinical References:**

**Chlamydia trachomatis and Neisseria gonorrhoeae, Nucleic Acid Amplification, Varies**

**Clinical Information:** Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection (STI) in the United States. In 2010, 1.3 million documented cases were reported to the CDC. Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adult. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual Chlamydia screening is now recommended for all sexually active women age 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given...
a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI, with 301,174 cases of gonorrhea reported to CDC in 2009. Like Chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases. Immunoassays and non-amplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis or Neisseria gonorrhoeae This test is not intended for use in medico-legal applications. This test is not useful for the detection of Chlamydia pneumoniae.

**Interpretation:** A positive result indicates that rRNA of Chlamydia trachomatis or Neisseria gonorrhoeae is present in the specimen tested and strongly supports a diagnosis of chlamydial or gonorrheal infection. A negative result indicates that rRNA for C trachomatis or N gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N gonorrhoeae), if appropriate. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of indeterminate indicates that a new specimen should be collected.

**Reference Values:**

- **Chlamydia trachomatis**
  - Negative

- **Neisseria gonorrhoeae**
  - Negative

**Clinical References:**

4. Gaydos CA, Quinn TC, Willis D,

**MCRNA 61554**  
**Chlamydia trachomatis, Miscellaneous Sites, Nucleic Acid Amplification, Varies**

**Clinical Information:** Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection in the United States. In 2010, 1.3 million documented cases were reported to the CDC. Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis infection. However, organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases. Immunoassays and non-amplification DNA tests are also available for C trachomatis detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis in non-FDA-approved specimen types. This test is not intended for use in medico-legal applications. This test is not useful for the detection of Chlamydia pneumoniae.

**Interpretation:** A positive result indicates the presence of rRNA Chlamydia trachomatis. This assay does detect plasmid-free variants of C trachomatis. A negative result indicates that rRNA for C trachomatis was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods, if appropriate.

**Reference Values:**  
Negative

**Chlamydia trachomatis, Nucleic Acid Amplification, Varies**

**Clinical Information:** Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection (STI) in the United States.\(^1,2\) In 2010, 1.3 million documented cases were reported to the Centers for Disease Control and Prevention (CDC).\(^2\) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile.\(^2\) Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection.\(^2\) Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure.\(^2\) Culture was previously considered to be the gold standard test for diagnosis of C trachomatis infection.\(^2\) However, organisms are labile in vitro and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.\(^3-5\) Immunoassays and non-amplification DNA tests are also available for C trachomatis detection, but these methods are significantly less sensitive and less specific than NAAT.\(^2\) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.\(^2\) Improved detection rates result from both the increased performance of the assay. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis This test is not intended for use in medico-legal applications. This test is not useful for the detection of Chlamydia pneumoniae.

**Interpretation:** A positive result indicates the presence of rRNA Chlamydia trachomatis. A negative result indicates that rRNA for C trachomatis was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods, if appropriate.

**Reference Values:**
- Negative

FCHLM
90343

Chlordane and Metabolites, Serum/Plasma

Reference Values:
Reporting limit determined each analysis

Alpha-Chlordane
Synonym(s): Cis-Chlordane
Results reported in ppb

Gamma-Chlordane
Synonym(s): Trans-Chlordane
Results reported in ppb

Trans-Nonachlor
Synonym(s): Chlordane Component
Results reported in ppb

Heptaclorepxoxide
Synonym(s): Chlordane Metabolite
Results reported in ppb

Oxychlordane
Synonym(s): Chlordane Metabolite
Results reported in ppb

Heptchlor
Synonym(s): Chlordane Component
Results reported in ppb

No reference data available.

CDP
8610

Chlordiazepoxide and Metabolite, Serum

Clinical Information: Chlordiazepoxide (Librium) is a benzodiazepine widely used in the treatment of anxiety, alcohol withdrawal symptoms, and as a premedication for anesthesia. The mechanism of action of all benzodiazepines remains unclear. However, it is known that benzodiazepines facilitate gamma-aminobutyric acid (GABA)-mediated neurotransmission in the brain. Benzodiazepines most likely facilitate the inhibitory presynaptic or postsynaptic reactions of GABA. Chlordiazepoxide is metabolized to long-acting metabolites in the liver to the active metabolite nordiazepam (desmethyldiazepam) and the clearance of the drug is reduced considerably in the elderly and in patients with hepatic disease. Therapeutic assessment should include measurement of both the parent drug (chlordiazepoxide) and the active metabolite (nordiazepam). Since chlordiazepoxide has a wide
therapeutic index and toxicity is dose-dependent, routine drug monitoring is not indicated in all patients.

**Useful For:** Monitoring chlordiazepoxide therapy Assessing toxicity

**Interpretation:** Chlordiazepoxide and nordiazepoxide combined concentrations above 5000 ng/mL have been associated with toxicity.

**Reference Values:**
Therapeutic concentration:
- Chlordiazepoxide: 400-3,000 ng/mL
- Nordiazepam: 100-500 ng/mL

**Clinical References:**

**Chloride, 24 Hour, Urine**

**Clinical Information:** Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium. Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride. However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

**Useful For:** An indicator of fluid balance and acid-base homeostasis using a 24-hour urine collection

**Interpretation:** Urine sodium and chloride excretion are similar, and, under steady-state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride. During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of sodium bicarbonate), while urine chloride excretion remains appropriately low.

**Reference Values:**
> or =18 years: 34-286 mmol/24 hours
Reference values have not been established for patients who are less than 18 years of age.

Reference values apply to 24-hour collection.

**Clinical References:**

**Chloride, Feces**

**Clinical Information:** The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector.
of this equilibrium. (1) Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Chronic diarrhea with elevations in fecal chloride concentrations are caused by congenital chloridorrhea. This is a rare condition associated with a genetic defect in a protein responsible for transport of chloride ions across the mucosal membranes in the lower intestinal tract in exchange for bicarbonate ions. It plays an essential part in intestinal chloride absorption, therefore variants in this gene have been associated with congenital chloride diarrhea. (2) Acquired chloridorrhea is a rare condition that has been described as causing profuse, chloride-rich diarrhea and a surprising contraction metabolic alkalosis rather than metabolic acidosis often associated with typical diarrhea. Contributors to acquired chloridorrhea include chronic intestinal inflammation and reduction of chloride/bicarbonate transporter expression in genetically susceptible persons post-bowel resection and ostomy placement. Acquired chloridorrhea is rare but may be an under-recognized condition in post-bowel resection patients. (3)

Useful For: Workup of cases of chronic diarrhea Evaluation of suspected chloridorrhea

Interpretation: Fecal chloride may be low (<20 mmol/L) in sodium sulfate-induced diarrhea. (4) Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea. (5)

Reference Values:
An interpretive report will be provided


Chloride, Random, Urine

Clinical Information: Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium. Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride. However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

Useful For: An indicator of fluid balance and acid-base homeostasis

Interpretation: Urine sodium and chloride excretion are similar and, under steady state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride. During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of sodium bicarbonate) while urine chloride excretion remains appropriately low.

Reference Values: No established reference values

Random urine chloride may be interpreted in conjunction with serum chloride, using both values to calculate fractional excretion of chloride.
The calculation for fractional excretion (FE) of chloride (Cl) is:

\[ \text{FE(Cl)} = \frac{\text{Cl} \ [\text{urine}] \times \text{Creat} \ [\text{serum}]}{\text{Cl} \ [\text{serum}] \times \text{Creat} \ [\text{urine}]} \times 100 \]

**Clinical References:**

**Chloride, Serum**

**Clinical Information:** Chloride is the major anion in the extracellular water space; its physiological significance is in maintaining proper body water distribution, osmotic pressure, and normal anion-cation balance in the extracellular fluid compartment. Chloride is increased in dehydration, renal tubular acidosis (hyperchloremia metabolic acidosis), acute renal failure, metabolic acidosis associated with prolonged diarrhea and loss of sodium bicarbonate, diabetes insipidus, adrenocortical hyperfunction, salicylate intoxication, and with excessive infusion of isotonic saline or extremely high dietary intake of salt. Hyperchloremia acidosis may be a sign of severe renal tubular pathology. Chloride is decreased in overhydration, chronic respiratory acidosis, salt-losing nephritis, metabolic alkalosis, congestive heart failure, Addisonian crisis, certain types of metabolic acidosis, persistent gastric secretion and prolonged vomiting, aldosteronism, bromide intoxication, syndrome of inappropriate antidiuretic hormone secretion, and conditions associated with expansion of extracellular fluid volume.

**Useful For:** Evaluation of water, electrolyte, and acid-base status

**Interpretation:** In normal individuals, serum chloride values vary little during the day, although there is a slight decrease after meals due to the diversion of chloride to the production of gastric juice.

**Reference Values:**
- 1-17 years: 102-112 mmol/L
- > or =18 years: 98-107 mmol/L

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

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

**Chlorpromazine (Thorazine)**

**Reference Values:**
Reference Range: 30 – 300 ng/mL

**Chocolate/Cacao IgG**

**Interpretation:**

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

**Cholecystokinin (CCK)**
Clinical Information: Cholecystokinin is a 33 amino acid peptide having a very similar structure to Gastrin. Cholecystokinin is present in several different sized forms including a 58 peptide Pro-CCK and 22, 12, and 8 peptide metabolites. The octapeptide retains full activity of the 33 peptide molecule. Cholecystokinin has an important physiological role in the regulation of pancreatic secretion, gallbladder contraction and intestinal motility. Cholecystokinin levels are elevated by dietary fat especially in diabetics. Elevated levels are seen in hepatic cirrhosis patients. Cholecystokinin is found in high levels in the gut, in the brain and throughout the central nervous system.

Reference Values:
Up to 80 pg/mL

CHLGP 608018

Cholestasis Gene Panel, Varies

Clinical Information: Cholestasis is a decrease in or obstruction of bile flow that results in jaundice, pruritus, hepatomegaly, and splenomegaly. Cholestasis can be the primary clinical symptom due to progressive familial intrahepatic cholestasis (PFIC) or one of a number of symptoms due to a variety of genetic disorders that cause multisystem disease. PFIC is a group of disorders caused by bile secretion or transport defects that result in intrahepatic cholestasis in infancy or childhood. There are 5 types of PFIC that are molecularly defined: FIC1 (ATP8B1 gene), PFIC2 (ABCB11 gene), PFIC3 (ABCB4 gene), PFIC4 (TJP2 gene), and PFIC5 (NR1H4 gene). PFICs 1, 2, and 4 have normal to mild elevations of gamma-glutamyltransferase (GGT). PFIC 3 results in significantly elevated serum GGT, whereas PFIC5 causes low to normal GGT levels. PFIC can present with cholestasis in neonates, but most commonly manifests around 3 months of age for those with PFIC2, the most common type. Studies of infants and children with cholestasis have shown that 12% to 13% have molecularly confirmed PFIC. Disease progression results in liver failure and hepatocellular carcinoma. Liver transplantation is an effective treatment, though less effective for multisystemic PFIC1 than for other types. However, there is significant mortality, as 87% of patients with untreated PFIC will not survive. A variety of other genetic disorders can also result in cholestasis, such as Alagille syndrome (JAG1 and NOTCH2 genes), alpha-1-antitrypsin deficiency (SERPINA1 gene), arthrogryposis, renal dysfunction, and cholestasis (ARC) syndrome (VPS33B and VIPAS39 genes), citrullinemia (SLC25A13 gene), congenital defects of bile acid synthesis (HSD3B7 and AKR1D1 genes), familial hypercholanemia (BAAT gene), neonatal ichthyosis-sclerosing cholangitis syndrome (CLDN1 gene), and Crigler-Najjar syndrome types I or II or Gilbert syndrome (UGT1A1). In addition, peroxisomal disorders (PEX genes) and mitochondrial disorders can include cholestatic liver disease among other features. A comprehensive gene panel is a rapid and reliable first-tier test to establish a diagnosis for patients with cholestasis.

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

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

Reference Values:
An interpretive report will be provided.

**Cholesterol, Body Fluid**

**Clinical Information:** Serum cholesterol is measured to determine the concentration of circulating lipoprotein particles when screening for cardiovascular disease. The concentration is affected by genetic and lifestyle factors. Cholesterol concentrations in serous effusions increase due to exudative processes that cause cell lysis or increased vascular permeability. Measurement of cholesterol in body fluids is used for the diagnosis of a cholesterol effusion or cholesterol-rich pseudochylous effusion. Pseudochylous effusions contain low triglycerides and high cholesterol and occur from chronic pleural effusions such as rheumatoid pleurisy and tuberculosis. Malignant effusions may become enriched with cholesterol due to increased synthesis and release from neoplastic cells or lymphatic obstruction. Pleural fluid: Chylothorax is the name given to pleural effusions containing chylomicrons with accordingly high triglyceride and low cholesterol concentrations, which occurs when chyle accumulates from a disruption of the thoracic duct caused mainly by malignancy or trauma. Pseudochylous effusions accumulate gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleurisy, tuberculosis, or myxedema, and by definition the effluent contains high concentrations of cholesterol, while chylous effusions contain high concentrations of triglycerides in the form of chylomicrons. Differentiation of pseudochylothorax from chylothorax is important as their milky or opalescent appearance is similar; however, therapeutic management strategies differ. Measurement of pleural fluid cholesterol has also been investigated in multiple studies for the purpose of differentiating exudates from transudates. Most of these studies concluded that cholesterol performs as well as measurement of lactate dehydrogenase and total protein applying Light's criteria, but does not add much value beyond that. Peritoneal fluid: Ascites is the pathologic accumulation of excess fluid in the peritoneal cavity. Cholesterol analysis in peritoneal fluid may be a useful index to separate malignant ascites from nonmalignant, often cirrhotic ascites. Studies report concentrations ranging from greater than 32 to 70 mg/dL are greater than 88% sensitive and greater than 80% specific for malignant ascites, outperforming cytology.

**Useful For:**
Aiding in the diagnosis of a cholesterol effusion or cholesterol-rich pseudochylous effusion in body fluids Distinguishing between chylous and pseudochylous pleural effusions Distinguishing between malignant and nonmalignant ascites

**Interpretation:**
Pleural fluid cholesterol concentrations between 45 to 65 mg/dL are consistent with exudative effusions. Cholesterol concentrations above 200 mg/dL suggest a pseudochylous effusion. Peritoneal fluid cholesterol concentrations between 32 to 70 mg/dL suggest a malignant cause of ascites.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

**Cholesterol, High-Density Lipoprotein (HDL), Serum**

**Clinical Information:** High-density lipoprotein (HDL) is the smallest of the lipoprotein particles and comprises a complex family of lipoprotein particles that exist in a constant state of dynamic flux as the particles interact with other HDL particles and with low-density lipoprotein (LDL) particles and very-low-density lipoprotein (VLDL) particles. HDL has the largest proportion of protein relative to lipid compared to other lipoproteins (>50% protein). Total cholesterol levels have long been known to be related to coronary heart disease (CHD). HDL cholesterol is also an important tool used to assess an
individual's risk of developing CHD since a strong negative relationship between HDL cholesterol concentration and the incidence of CHD has been reported. In some individuals, exercise increases the HDL cholesterol level; those with more physical activity have higher HDL cholesterol values.

**Useful For:** Cardiovascular risk assessment

**Interpretation:** Low high-density lipoprotein (HDL) cholesterol correlates with increased risk for coronary heart disease (CHD). Values greater than or equal to 80 to 100 mg/dL may indicate metabolic response to certain medications such as hormone replacement therapy, chronic liver disease, or some form of chronic intoxication, such as with alcohol, heavy metals, or industrial chemicals including pesticides. HDL values of 5 mg/dL or less occur in Tangier disease, in association with cholestatic liver disease, and in association with diminished hepatocyte function. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

- **HDL CHOLESTEROL**
  - Males: > or =40 mg/dL
  - Females: > or =50 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17:

- **HDL CHOLESTEROL**
  - Low HDL: <40 mg/dL
  - Borderline low: 40-45 mg/dL
  - Acceptable: >45 mg/dL

**Clinical References:**

**CHOL 8320**

**Cholesterol, Total, Serum**

**Clinical Information:** Cholesterol is a steroid with a secondary hydroxyl group in the C3 position. It is synthesized in many types of tissue, but particularly in the liver and intestinal wall. Approximately 75% of cholesterol is newly synthesized and 25% originates from dietary intake. Normally, the cholesterol in the plasma or serum is 60% to 80% esterified. Approximately 50% to 75% of the plasma cholesterol is transported by low-density lipoproteins (LDL) and 15% to 40% by high-density lipoproteins (HDL). Serum cholesterol is elevated in the hereditary hyperlipoproteinemias and in various other metabolic diseases. Moderate-to-markedly elevated values are also seen in cholestatic liver disease. Hypercholesterolemia reflects an increase of lipoproteins of 1 or more specific classes (eg, beta-LDL, alpha-1 HDL, alpha-2 HDL, or LP-X). Hypercholesterolemia is a risk factor for cardiovascular disease. Low levels of cholesterol can be seen in disorders that include hyperthyroidism, malabsorption, and deficiencies of apolipoproteins.

**Useful For:** Evaluation of cardiovascular risk

**Interpretation:** The National Lipid Association and the National Cholesterol Education Program
(NCEP) have set the following guidelines for total cholesterol: Desirable: <200 mg/dL Borderline high: 200 to 239 mg/dL. High: > or =240 mg/dL. Values above the normal range indicate a need for quantitative analysis of the lipoprotein profile. Values in hyperthyroidism usually are in the lower normal range; malabsorption values may be below 100 mg/dL, while beta-lipoprotein or apolipoprotein B deficiency values usually are below 80 mg/dL. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

**TOTAL CHOLESTEROL**
Desirable: <200 mg/dL
Borderline high: 200-239 mg/dL
High: > or =240 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children 2 to 17 years of age:

**TOTAL CHOLESTEROL**
Acceptable: <170 mg/dL
Borderline high: 170-199 mg/dL
High: > or =200 mg/dL


**CHLE**

**8324**

**Cholesteryl Esters, Serum**

**Clinical Information:** Cholesterol in the blood serum normally is 60% to 80% esterified with fatty acids, largely as a result of the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which circulates in the blood in association with the high-density lipoproteins. LCAT transfers an acyl group for lecithin to cholesterol. Familial deficiency of LCAT is uncommon, usually occurring individuals of northern Europe descent, and is associated with erythrocyte abnormalities (target cells) and decreased (20% or less) esterification of plasma cholesterol. This is associated with early atherosclerosis, corneal opacification, hyperlipidemia, and mild hemolytic anemia. Persons with liver disease may have impaired formation of LCAT and, therefore, a secondary deficiency of this enzyme and of esterified plasma cholesterol.

**Useful For:** Establishing a diagnosis of lecithin-cholesterol acyltransferase deficiency Evaluating the extent of metabolic disturbance by bile stasis or liver disease

**Interpretation:** In patients with lecithin-cholesterol acyltransferase deficiency, the concentration of unesterified cholesterol in serum may increase 2 to 5 times the normal value, resulting in a decrease in esterified serum cholesterol to 20% or less of the total serum cholesterol.

**Reference Values:**
60-80% of total cholesterol
Reference values have not been established for patients that are <16 years of age.

**Clinical References:** Glomset JA, Assmann G, Gjone E, Norum KR: Lecithin: cholesterol
Chromatin (Nucleosomal) Antibody

Reference Values:

Reference Range:          <1.0 Negative AI

Chromium and Cobalt, Synovial Fluid

Clinical Information: Per FDA recommendations, orthopedic surgeons should consider measuring and following serial chromium (Cr) and cobalt (Co) concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. However, a recent publication(1) has shown synovial fluid measurements were superior to whole blood and serum Cr and Co concentrations in predicting local tissue destruction in failed hip arthroplasty constructs. Prosthetic devices produced by Deupuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of Cr, Co, and molybdenum. This list of products is incomplete, and the products' compositions change occasionally; see each prostheses' product information for composition details. Cr: Cr is a naturally-occurring element widely distributed in the environment. It exists in several valence states with the 3 main forms being Cr(0), Cr(III), and Cr(VI). Cr(III) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Cr is widely used in manufacturing processes to make various metal alloys such as stainless steel. It is also used in many consumer products including: wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. The general population is most likely to be exposed to trace levels of Cr, as Cr(III) is naturally occurring in foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. Co: Co is a naturally occurring, hard, grey element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Co is an essential cofactor in vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of Co intake. However, more than a million workers are potentially exposed to Co and its compounds, with the greatest exposure in mining processes, cemented tungsten-carbide industry, Co powder industry, and alloy production industry. Co is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic exposure to Co-containing hard metal (dust or fume) can result in a serious lung disease called "hard metal lung disease," which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of Co particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to Co is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. In cases of suspected toxicity, blood, serum, or urine concentrations of Co can be checked. Vitamin B12 should be used to assess nutritional status.

Useful For: Monitoring metallic prosthetic implant wear and local tissue destruction in failed hip arthroplasty constructs This test is not useful for assessment of vitamin B12 activity.

Interpretation: Chromium: Based on an internal study, synovial fluid chromium concentrations of 17.1 ng/mL or above were more likely due to a metal reaction (eg adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 84.6% and specificity of 85.2%). Cobalt: Based on an internal study, synovial fluid cobalt concentrations of 17.2 ng/mL or above were more likely due to a metal reaction (eg, adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 80.8% and specificity of...
81.5%)

Reference Values:
CHROMIUM:
0-17 years: Not established
> or =18 years: <17.1 ng/mL

COBALT:
0-17 years: Not established
> or =18 years: <17.2 ng/mL


CRUO 65719

Chromium Occupational Exposure, Random, Urine

Clinical Information: Chromium (Cr) has an atomic mass of 51.996, atomic number 24, and valences ranging from 2(-) to 6(+). Hexavalent chromium, Cr(6+), and trivalent chromium, Cr(3+), are the 2 most prevalent forms. Cr(3+) is the only oxidation state present under normal physiologic conditions. Cr(6+) is widely used in industry to make chromium alloys including stainless steel pigments and electroplated coatings. Cr(6+), a known carcinogen, is rapidly metabolized to Cr(3+). Cr(3+) is the only form present in human urine.

Useful For: Screening for occupational exposure

Interpretation: The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure.(1) They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively (Section 3.3.1).

Reference Values:
0-17 years: not established
> or =18 years: The American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index (BEI) for daily occupational exposure to hexavalent chromium in urine is an increase of 10.0 mcg/L between pre-shift and post-shift urine collections. The ACGIH BEI for long- and short-term hexavalent chromium in urine is an end-of-shift concentration of >24.9 mcg/L at the end of the work week.


CRU 8593

Chromium, 24 Hour, Urine

Clinical Information: Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[6+]) and trivalent chromium (Cr[3+]) are the 2 most prevalent forms. Cr(6+) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings.
Cr(6+), a known carcinogen, is immediately converted to Cr(3+) upon exposure to biological tissues. Cr(3+) is the only chromium species found in biological specimens. Urine chromium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Screening for occupational exposure to chromium Monitoring metallic prosthetic implant wear

**Interpretation:** Chromium is principally excreted in the urine. Urine levels correlate with exposure. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (8-16 mcg/24 hour) in urine chromium concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations greater than 20 mcg/24 hours in a patient with chromium-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. A test for this specific purpose (CROMU / Chromium for Occupational Monitoring, Random, Urine) is available.

**Reference Values:**
0-17 years: not established
> or =18 years: 0.1-1.2 mcg/24 hours

**Clinical References:**

**Chromium, Blood**

**Clinical Information:** Chromium (Cr) is a naturally occurring element widely distributed in the environment. Chromium exists in several valence states with the 3 main forms being Cr(0), Cr(III), and Cr(VI). Cr(III) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Chromium is widely used in manufacturing processes to make various metal alloys such as stainless steel. It is also used in many consumer products including: wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. The general population is most likely to be exposed to trace levels of chromium in the food that is eaten. Low levels of Cr(III) occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. Per FDA recommendations, orthopedic surgeons should consider measuring and following serial chromium concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. Blood Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.
Useful For: Monitoring exposure to chromium using whole blood specimens Monitoring metallic prosthetic implant wear

Interpretation: Results greater than the reference range indicate exposure to chromium (Cr) (see Cautions about specimen collection). Prosthesis wear is known to result in increased circulating concentration of metal ions. Increased blood trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0-17 years: not established
> or =18 years: <1.0 ng/mL

Clinical References:

Chromium, Serum

Clinical Information: Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[+6]) and trivalent chromium (Cr[+3]) are the 2 most prevalent forms. Cr(+6) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(+6), a known carcinogen, is immediately converted to Cr(+3) upon exposure to biological tissues. Cr(+3) is the only chromium species found in biological specimens. Serum Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricron, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Screening for occupational exposure Monitoring metallic prosthetic implant wear

Interpretation: Results greater than the flagged value indicate clinically significant exposure to chromium (Cr) (see Cautions about specimen collection). The reported units of measurement for chromium of ng/mL is equivalent to mcg/L. Prosthesis wear is known to result in an increased circulating concentration of metal ions. A modest increase (0.3-0.6 ng/mL) in serum Cr concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 1 ng/mL in a patient with a Cr-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. However, the FDA recommends testing chromium in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal implants.

Reference Values:
<0.3 ng/mL

When collected by a phlebotomist experienced in ultra-clean collection technique and handled according to the instructions in Trace Metals Analysis Specimen Collection and Transport in Special
Instructions, we have observed the concentration of chromium in serum to be <0.3 ng/mL. However, the majority of specimens submitted for analysis from unexposed individuals contain 0.3 ng/mL to 0.9 ng/mL of chromium. Commercial evacuated blood collection tubes not designed for trace-metal specimen collection yield serum containing 2.0 ng/mL to 5.0 ng/mL chromium derived from the collection tube.

**Clinical References:**
2. NIOSH Hexavalent Chromium Criteria Document Update. September 2008; Available at www.cdc.gov/niosh/topics/hexchrom/

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**Chromium, Synovial Fluid**

**Clinical Information:** Chromium (Cr) is a naturally-occurring element widely distributed in the environment. It exists in several valence states with the 3 main forms being Cr(0), Cr(III), and Cr(VI). Cr(III) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Cr is widely used in manufacturing processes to make various metal alloys such as stainless steel. It is also used in many consumer products including: wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. Per FDA recommendations, orthopedic surgeons should consider measuring and following serial chromium concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. However, a recent publication(1) has shown synovial fluid measurements were superior to whole blood and serum Cr concentrations in predicting local tissue destruction in failed hip arthroplasty constructs. Prosthetic devices produced by Deupuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of Cr, cobalt, and molybdenum. This list of products is incomplete, and the products' compositions change occasionally; see each prostheses' product information for composition details. The general population is most likely to be exposed to trace levels of Cr, as Cr(III) is naturally occurring in foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. In cases of suspected toxicity, blood, serum, or urine concentrations of chromium can be checked.

**Useful For:** Monitoring metallic prosthetic implant wear and local tissue destruction in failed hip arthroplasty constructs. This test is not useful for assessment of potential chromium toxicity.

**Interpretation:** Based on an internal study, synovial fluid chromium concentrations of 17.1 ng/mL or above were more likely due to a metal reaction (eg adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 84.6% and specificity of 85.2%).

**Reference Values:**
- 0-17 years: Not established
- ≥18 years: <17.1 ng/mL

**Clinical References:**
1. Houdek MT, Wyles CC, Jannetto PJ, et al: Synovial fluid metal levels are superior to whole blood and serum metal ion levels in predicting local tissue destruction in failed hip arthroplasty constructs. Orthopaedic Proceed. 2018;100-B(SUPP_1):39
Chromium/Creatinine Ratio, Random, Urine

Clinical Information: Chromium (Cr) has an atomic mass of 51.996, atomic number 24, and valences ranging from 2(-) to 6(+). Hexavalent chromium, Cr(6+), and trivalent chromium, Cr(3+), are the 2 most prevalent forms. Cr(3+) is the only oxidation state present under normal physiologic conditions. Cr(6+) is widely used in industry to make chromium alloys including stainless steel pigments and electroplated coatings. Cr(6+), a known carcinogen, is rapidly metabolized to Cr(3+). Cr(3+) is the only form present in human urine.

Useful For: Detecting chromium exposure

Interpretation: Chromium is principally excreted in the urine. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. The National Institute for Occupational Safety and Health (NIOSH) document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. The biological exposure indices (BEI) for total chromium in urine measured at the end of the shift at the end of the workweek is 25 mcg/L. The BEI for the increase in total chromium during a shift is 10 mcg/L. A test for this specific purpose (CROMU / Chromium for Occupational Monitoring, Random, Urine) is available.

Reference Values:
0-17 years: not established
>17 years: <0.8 mcg/g Creatinine

Clinical References:

Chromogenic Factor IX Activity Assay, Plasma

Clinical Information: Factor IX (FIX) is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital FIX deficiency is inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) characterized by hemorrhhoses, deep tissue bleeding, excessive bleeding with trauma, and ecchymoses. Typically, these patients are tested using a 1-stage clotting assay. However, new treatment options using long-acting glycoPEGylated replacement products are being approved for clinical use. Pharmacokinetic studies for these products indicate ideal monitoring of patients should be performed by the 2-stage chromogenic assay.

Useful For: Monitoring coagulation factor replacement therapy of selected extended half-life coagulation factor replacements Aiding in the diagnosis of hemophilia B using a 2-stage assay, especially when a 1-stage assay was normal

Interpretation: Factor IX deficiency may be acquired (eg, vitamin K deficiency, warfarin anticoagulation effect, liver disease, or a consumptive coagulopathy) or congenital (hemophilia B). Optimal laboratory monitoring of selected extended half-life factor IX replacement therapy (eg, glycoPEGylated factor FIX) may be achieved with the chromogenic factor IX assay. Elevated factor IX levels may be associated with acute or chronic inflammation, excess factor IX replacement therapy, or as a result of a rare genetic variant, factor IX Padua.

Reference Values:

Chromogenic Factor IX activity generally correlates with the one-stage FIX activity. In full
term/premature neonates, infants, children, and adolescents the one-stage FIX activity* is similar to
adults. However, no similar data for chromogenic FIX activity are available. (Appel JTH 2012;
10:2254)

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and
Processing in Special Instructions.

noacog beta pegol with commercially available one-stage clotting and chromogenic assay kits: a
Signer-Romero K, Key NS: Current laboratory practices in the diagnosis and management of
Ezban M: Factor IX-deficient plasma spiked with N9-GP behaves similarly to N9-GP post-administration
labelling and postinfusion testing: challenges for caregivers and regulators. Haemophilia 2015
one-stage clotting and chromogenic assays. Haemophilia 2014 Nov;20(6):891-897

Chromogenic Factor VIII Activity Assay, Plasma

Clinical Information: Factor VIII (FVIII) is synthesized in the endothelial cells of the liver and,
perhaps, in other tissues. It is a coagulation cofactor that circulates bound to von Willebrand factor and is
part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours).
Congenital FVIII deficiency is inherited in a recessive X-linked manner and results in hemophilia A,
which has an incidence of 1 in 10,000 live male births. Patients with severe deficiency (<1%) experience
spontaneous bleeding episodes (eg, hemarthrosis, deep-tissue bleeding, etc), whereas patients with
moderate or mild deficiency (>1%) typically experience post-trauma or surgical bleeding. FVIII activity
assays (FVIII:C) are performed to diagnose hemophilia A and to monitor FVIII replacement therapy.
FVIII:C assays are typically 1-stage clotting assays. However, there is a subset of patients with mild
hemophilia A who have shown discrepantly low results when measured with the 2-stage (chromogenic)
assay, indicating that testing patients with a mild bleeding history with both a 1- and 2-stage assay would
aid in diagnosis. In addition, there are new treatment options using long-acting glycoPEGylated products.
Pharmacokinetic studies are showing that ideal monitoring of patients should be performed by the 2-stage
chromogenic assay.

Useful For: Monitoring coagulation factor replacement therapy of selected extended half-life
coaulation factor replacements Aiding in the diagnosis of hemophilia A using a 2-stage assay, especially
when the 1-stage assay was normal

Interpretation: Factor VIII deficiency may be seen in congenital hemophilia A, acquired
(autimmune) hemophilia A, or von Willebrand disease (congenital and acquired). Laboratory artifacts
that may result in artificially reduced factor VIII include samples collected in EDTA, instead of citrate, or
heparin contamination of the plasma sample. Elevated factor VIII may be seen in acute or chronic
inflammatory states or excess factor VIII replacement therapy.

Reference Values:
55.0-200.0%

Chromogenic Factor VIII activity generally correlates with the one-stage FVIII activity. In full
term/premature neonates, infants, children, and adolescents the one-stage FVIII activity* is similar to
adults. However, no similar data for chromogenic FVIII activity are available.(Appel JTH 2012;10:2254)

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and
Processing in Special Instructions.

**CH8BI**  
**Chromogenic Factor VIII Inhibitor Bethesda Profile**  
**Interpretation**

**Clinical Information:** Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may be alloimmune: developing in patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate or autoimmue: occurring in patients without hemophilia (not previously factor VIII deficient) either spontaneously or during pregnancy or in association with autoimmune diseases.

**Useful For:** Interpretation of CHF8P / Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma  
Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII  
This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.

**Interpretation:** The interpretive report will include assay information, background information, and conclusions based on the test results.

**Reference Values:**  
Only orderable as part of a profile. For more information see CHF8P / Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma.  
An interpretive report will be provided.


**CHF8P**  
**Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma**

**Clinical Information:** Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may be alloimmune: developing in patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate or autoimmune: occurring in patients without hemophilia (not previously factor VIII deficient) either spontaneously, during pregnancy, or in association with autoimmune diseases.

**Useful For:** Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII for patients on emicizumab (Hemlibra)  
Detecting the presence and titer of an inhibitor directed against factor VIII. This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Chromogenic Factor VIII Activity Assay (CHF8)
- Adults: 55.0-200.0%
- Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

BETHESDA TITER (CH8B)
< or =0.5 Bethesda Units

**Clinical References:**

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**Chromogenic Factor VIII Inhibitor Bethesda Titer, Plasma**

**Clinical Information:** Factor VIII inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may be alloimmune: developing in patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate or autoimmune: occurring in nonhemophiliac patients (not previously factor VIII deficient) either spontaneously, during pregnancy, or in association with autoimmune diseases.

**Useful For:** Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII. This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.

**Interpretation:** The interpretive report will include assay information, background information, and conclusions based on the test results.

**Reference Values:**
Only orderable as part of a profile. For more information see CH8BP / Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma.

< or =0.5 Bethesda Units

**Clinical References:**

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**Chromogranin A, Serum**

**Clinical Information:** Chromogranin A (CGA) is a 439-amino acid protein with a molecular weight of 48 to 60 kDa, depending on glycosylation and phosphorylation status. It is a member of the granin family of proteins and polypeptides. Granins are widespread in endocrine, neuroendocrine, peripheral, and central nervous tissues, where they are found in secretory granules alongside the tissue-specific secretion products. The role of granins within the granules is to maintain the regulated secretion of these signaling molecules. This includes: -Facilitating the formation of secretory granules -Calcium- and pH-mediated...
sequestration and resolubilization of hormones or neurotransmitters. Regulation of neuropeptide and peptide hormone processing through modulation of prohormone convertase activity. In addition, granins contain multiple protease and peptidase cleavage sites and, upon intra- or extracellular cleavage, give rise to a series of daughter peptides with distinct extracellular functions. Some of these have defined functions, such as pancreastatin, vasostatin, and catestatin, while others are less well characterized. Because of its ubiquitous distribution within neuroendocrine tissues, CGA can be a useful diagnostic marker for neuroendocrine neoplasms, including carcinoids, pheochromocytomas, neuroblastomas, medullary thyroid carcinomas (MTC), some pituitary tumors, functioning and nonfunctioning islet cell tumors, and other amine precursor uptake and decarboxylation (APUD) tumors. It can also serve as a sensitive means for detecting residual or recurrent disease in treated patients. Carcinoid tumors in particular almost always secrete CGA along with a variety of specific modified amines, chiefly serotonin (5-hydroxytryptamine: 5-HT) and peptides. Carcinoid tumors are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines and peptide hormones secreted, as to local and distant spread. The symptoms of this carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. Serum CGA and urine 5-hydroxyindolacetic acid (5-HIAA) are considered the most useful biochemical markers and are first-line tests in disease surveillance of most patients with carcinoid tumors. Serum CGA measurements are used in conjunction with, or alternative to, measurements of serum or whole blood serotonin, urine serotonin and 5-HIAA, and imaging studies. This includes the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing. Finally, a number of tumors that are not derived from classical endocrine or neuroendocrine tissues, but contain cells with partial neuroendocrine differentiation, such as small-cell carcinoma of the lung or prostate carcinoma, may also display elevated CGA levels. The role of CGA measurement is not well defined in these tumors, with the possible exception of prognostic information in advanced prostate cancer.

**Useful For:** Follow-up or surveillance of patients with known or treated carcinoid tumors. An adjunct in the diagnosis of carcinoid tumors. An adjunct in the diagnosis of other neuroendocrine tumors, including pheochromocytomas, medullary thyroid carcinomas, functioning and nonfunctioning islet cell and gastrointestinal amine precursor uptake and decarboxylation tumors, and pituitary adenomas. A possible adjunct in outcome prediction and follow-up in advanced prostate cancer.

**Interpretation:** Follow-up/Surveillance: Urine 5-hydroxyindolacetic acid (5-HIAA) and serum chromogranin A (CGA) increase in proportion to carcinoid tumor burden. Because of the linear relationship of CGA to tumor burden, its measurement also provides prognostic information. Most midgut and hindgut tumors secrete CGA even if they do not produce significant amounts of serotonin or serotonin metabolites (5-HIAA). Guidelines recommend 3 to 12 monthly measurements of CGA or 5-HIAA in follow-up of midgut carcinoids. Patients with foregut tumors can also be monitored with CGA or 5-HIAA measurements, if they were positive for these markers at initial diagnosis. Hindgut tumors usually do not secrete serotonin and consequently, only CGA monitoring is recommended. As is typical for tumor marker use in follow-up and surveillance, a 40% to 50% change in serum CGA concentrations should be considered potentially clinically significant in the absence of confounding factors (see Cautions). Much smaller changes in CGA concentrations might be considered significant if they occur over several serial measurements and are all in the same direction. Adjunct in Diagnosis of Carcinoid Tumors: CGA is elevated in most patients (approximately 90%) with symptomatic or advanced carcinoids (carcinoid syndrome), usually to levels several times the upper limit of the reference interval. Serum CGA measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. CGA is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. To achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serum CGA, serotonin in serum or blood, and 5-HIAA in urine should all be measured. In most cases, if none of these 3 analytes are elevated, carcinoids can usually be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests such as urine serotonin measurement will be required. An example would be a foregut tumor that does not secrete CGA and only produces 5-hydroxytryptophan (5-HTP) rather than serotonin. In this case, circulating chromogranin, serotonin, and urine 5-HIAA
levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels. Adjunct in the Diagnosis of Other Neuroendocrine Tumors: In patients with suspected neuroendocrine tumors other than carcinoids, CGA is often elevated alongside any specific amine and peptide hormones or neurotransmitters that may be produced. The CGA elevations are less pronounced than in carcinoid tumors, and measurement of specific tumor secretion products is considered of greater utility. However, CGA measurements can occasionally aid in diagnosis of these tumors if specific hormone measurements are inconclusive. This is the case in particular with pheochromocytoma and neuroblastoma, where CGA levels may be substantially elevated and can, therefore, provide supplementary and confirmatory information to measurements of specific hormones. In particular, CGA measurements might provide useful diagnostic information in patients with mild elevations in catecholamines and metanephrines; such mild elevations often represent false-positive test results. Possible Adjunct in Outcome Prediction and Follow-up of Prostate Cancer: Prostate cancers often contain cells with partial neuroendocrine differentiation. These cells secrete CGA. The amounts secreted are insufficient in most cases to make this a useful marker for prostate cancer diagnosis. However, if patients with advanced prostate cancer are found to have elevated CGA levels, this indicates the tumor contains a significant neuroendocrine cell subpopulation. Such tumors are often resistant to antiandrogen therapy and have a worse prognosis. These patients should be monitored particularly closely.

Reference Values:
<93 ng/mL
Reference values apply to all ages.

Clinical References:

Chromogranin Immunostain, Technical Component Only

Clinical Information: Chromogranin A is widely expressed in neuronal tissues and in secretory granules of human endocrine cells such as parathyroid gland, adrenal medulla, anterior pituitary gland, Langerhans islets of the pancreas, and C-cells of the thyroid. It is useful for the identification of tumors with neuroendocrine differentiation such as pituitary adenomas, islet cell tumors, pheochromocytomas, medullary thyroid carcinomas, Merkel cell tumors, and carcinoids.

Useful For: Aiding in the identification of tumors with neuroendocrine differentiation

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is
available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of
the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
antibody against human chromogranin A for immunohistochemical diagnosis. BMC Biotechnology.
2018 May;18(1):25
2. Kyriakopoulos G, Mavroedi V, Chatzellis E, Kaltetas GA, Alexandraki KI:
Histopathological, immunohistochemical, genetic and molecular markers of neuroendocrine neoplasms.
Ann Transl Med. 2018 Jun;6(12):252
3. Gkolfinopoulos S, Tsapakidis K, Papadimitriou K,
Papamichael D, Kountourakis P: Chromogranin A as a valid marker in oncology: Clinical application or

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**CMAFF 35263**

**Chromosomal Microarray (CMA) Familial Testing, FISH**

**Clinical Information:** Chromosomal microarray (CMA) is a method for detecting copy number
changes (gains or losses) across the entire genome. When copy number changes are identified in a
patient, parental studies are sometimes necessary to assess their clinical significance. Changes that are
inherited from clinically normal parents are less likely to be clinically significant in the patient and de
novo changes are more likely to be pathogenic. To identify familial copy number changes in parents of
previously tested patients, FISH testing is utilized. The parental results will provide the context for
interpretation of the patient's CMA results.

**Useful For:** Determining the inheritance pattern of copy number changes previously identified by
chromosomal microarray analysis in a patient and aiding in the clinical interpretation of the
pathogenicity of the copy number change

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. J Pediatr
2006 Jul;149(1):98-102
relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. Genet
Med 2008 May;10:415-429

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**CMAPOC 63042**

**Chromosomal Microarray, Autopsy, Products of Conception,
or Stillbirth, Varies**

**Clinical Information:** Chromosomal abnormalities may result in malformed fetuses, spontaneous
abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in
spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of
products of conception (POC), a stillborn infant, or neonate (autopsy) may provide useful information
concerning the cause of fetal loss. In addition, CMA may provide information regarding the recurrence
risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This
is particularly useful information if there is a family history of 2 or more miscarriages or when fetal
malformations are evident. CMA is a high-resolution method for detecting copy number changes (gains
or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype.
This CMA test utilizes more than 1.9 million copy number probes and approximately 750,000 single
nucleotide polymorphism probes for the detection of copy number changes and regions with absence of
heterozygosity. Identification of regions of excess homozygosity on a single chromosome could suggest
uniparental disomy that may warrant further clinical investigation when observed on chromosomes with
known imprinting disorders. In addition, the detection of excess homozygosity on multiple
chromosomes may suggest consanguinity.

**Useful For:** Prenatal diagnosis of copy number changes (gains or losses) across the entire genome
Diagnosing chromosomal causes for fetal death Determining recurrence risk of future pregnancy losses
Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and fluorescence in situ hybridization (FISH) studies. Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray. Assessing regions of homozygosity related to uniparental disomy or identical by descent.

**Interpretation:** Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes but is not limited to incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics (ACMG). (1) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 1 megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy (UPD) or to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Regions with absence of heterozygosity (AOH) of unknown significance will be reported when greater than 5 Mb (terminal) and 10 Mb (interstitial) on UPD-associated chromosomes. Whole genome AOH will be reported when greater than 10% of the genome. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CMAMT 62667 Chromosomal Microarray, Autopsy/Products of Conception/Stillbirth, Tissue**

**Clinical Information:** Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of products of conception (POC), a stillborn infant, or a neonate (autopsy) may provide useful information concerning the cause of miscarriage or fetal loss. In addition, CMA may provide information regarding the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages or when fetal malformations are evident. CMA is a high-resolution method for detecting copy number changes (gains or losses)
losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes over 220,000 markers for the detection of copy number changes and regions with absence of heterozygosity. The detection of excess homozygosity on multiple chromosomes may suggest consanguinity. Homozygosity involving the entire genome is indicative of a complete molar pregnancy.

**Useful For:** Diagnosis of congenital copy number changes in products of conception, including aneuploidy (i.e., trisomy or monosomy) and structural abnormalities. Diagnosing chromosomal causes for fetal death. Determining recurrence risk of future pregnancy losses. Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected previously by other methods such as conventional chromosome and fluorescence in situ hybridization (FISH) studies. Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray.

**Interpretation:** Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes, but is not limited to, incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics (ACMG). Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 1 megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Homozygosity will be reported when involving greater than 20% of the genome. Homozygosity involving the entire genome is indicative of a complete molar pregnancy. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
chromosome analysis. However, many pathogenic rearrangements are below the resolution limits of chromosome analysis (approximately 5 megabases). Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes greater than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions of excessive homozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy (UPD), which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders associated with UPD. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity and, therefore, could be useful in determining candidate genes for further testing for autosomal recessive disorders. An online research opportunity called GenomeConnect (genomeconnect.org) is available for the recipients of genetic test results. This patient registry collects deidentified genetic and health information to advance knowledge of genetic variants. See GenomeConnect Patient Portal in Special Instructions for more information.

**Useful For:** First-tier, postnatal testing for individuals with multiple anomalies that are not specific to well-delineated genetic syndromes, apparently nonsyndromic developmental delay or intellectual disability, or autism spectrum disorders as recommended by the American College of Medical Genetics and Genomics (ACMG) Follow-up testing for individuals with unexplained developmental delay or intellectual disability, autism spectrum disorders, or congenital anomalies with a previously normal conventional chromosome study Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and fluorescence in situ hybridization (FISH) studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identity by descent

**Interpretation:** When interpreting results, the following factors need to be considered: Copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance pattern, and the clinical and/or developmental history of a transmitting parent. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes but is not limited to incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics (ACMG).(1) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 200 kilobases (kb) or a duplication greater than 1 megabase (Mb). The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy (UPD) or to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Interstitial regions with absence of heterozygosity (AOH) of unknown significance will be reported when greater than 10 Mb on UPD-associated chromosomes, and greater than 15 Mb on non-imprinted chromosomes. Terminal AOH will be reported when greater than 5 Mb. Whole genome AOH will be reported when greater than 2% of the genome. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Families benefit from hearing genetic information multiple times and in multiple ways. A referral to a clinical genetics professional is appropriate for individuals and families to discuss the results of chromosomal microarray testing.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** 1. Kalia, S., Adelman, K., Bale, S. et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing. 2016 update (ACMG SF v2.0): a policy
CMAH 35899

Chromosomal Microarray, Hematologic Disorders, Varies

Clinical Information: The importance of identifying chromosome abnormalities in hematologic disorders is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can do the following: - Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities - Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies - Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances - Assess regions of copy-neutral loss of heterozygosity which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Detection and characterization of clonal copy number imbalance and loss of heterozygosity associated with hematologic neoplasms Assisting in the diagnosis and classification of certain hematologic neoplasms Evaluating the prognosis for patients with certain hematologic neoplasms

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (e.g., XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.
Reference Values:
An interpretive report will be provided.


Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling

Clinical Information: Chromosomal abnormalities cause a wide range of disorders associated with birth defects and intellectual disability. Many of these disorders can be diagnosed prenatally by analysis of chorionic villi or amniocytes. The most common reasons for performing cytogenetic studies for prenatal diagnosis include advanced maternal age, abnormal prenatal screen, a previous child with a chromosome abnormality, abnormal fetal ultrasound, or a family history of a chromosome abnormality. Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the chromosomal microarray as a replacement for the fetal karyotype in patients with a pregnancy demonstrating one or more major structural abnormalities on ultrasound when undergoing invasive prenatal diagnosis.(1) This CMA test utilizes more than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy, which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity.

Useful For: Prenatal diagnosis of copy number changes (gains or losses) across the entire genome Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and fluorescence in situ hybridization (FISH) studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identity by descent

Interpretation: Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. When interpreting results it is important to realize that copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance pattern, and the clinical and developmental history of a transmitting parent. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes but is not limited to incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics (ACMG).(2) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 1
megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy (UPD) or to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Regions with absence of heterozygosity (AOH) of unknown significance will be reported when greater than 5 Mb (terminal) and 10 Mb (interstitial) on UPD-associated chromosomes. Whole genome AOH will be reported when greater than 10% of the genome. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding.

**Reference Values:**
An interpretive report will be provided.


**CMAPT**
**Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded**

**Clinical Information:** The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes copy number probes and single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 50 to 100 kilobases. CMA can: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

**Useful For:** Genomic characterization of tumor for copy number imbalances and loss of heterozygosity Assisting in the diagnosis and classification of malignant neoplasms Evaluating the prognosis for patients with malignant tumors

**Interpretation:** The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenic evolution will be discussed if identified. The continual discovery of novel copy number

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variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties. See Cytogenetic Analysis of Glioma in Special Instructions for common questions and answers.

Reference Values:
An interpretive report will be provided.

Clinical References:

CMAT 35900
Chromosomal Microarray, Tumor, Fresh or Frozen using Affymetrix Cytoscan HD

Clinical Information: The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes greater than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can: Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Genomic characterization of tumor for copy number imbalances and loss of heterozygosity Assisting in the diagnosis and classification of malignant neoplasms, including hematolymphoid malignancies Evaluating the prognosis for patients with malignant tumors

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen
collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

Reference Values:
An interpretive report will be provided.


CHRAF 35243  
**Chromosome Analysis, Amniotic Fluid**

**Clinical Information:** Chromosome analysis for prenatal diagnosis is appropriate in pregnancies with abnormal maternal screening, advanced maternal age, and features suggestive of or concerns for aneuploidy syndromes, including Down syndrome, Turner syndrome, Klinefelter syndrome, trisomy 13 syndrome, and trisomy 18 syndrome. Chromosomal abnormalities are the cause of a wide range of disorders associated with birth defects and congenital diseases. Many of these disorders can be diagnosed prenatally by analysis of amniocytes. This method permits diagnosis of chromosome abnormalities during the second trimester of pregnancy or later. A chromosomal microarray (CMA/Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling) is recommended, rather than chromosomal analysis, to detect clinically relevant gains or losses of chromosomal material in pregnancies with 1 or more major structural abnormalities. Chromosomal microarray can also be considered, rather than chromosome analysis, for patients undergoing invasive prenatal diagnostic testing with a structurally normal fetus.

Useful For: Prenatal diagnosis of chromosome abnormalities, including aneuploidy ( ie, trisomy or monosomy) and balanced rearrangements

Interpretation: Cytogenetic studies on amniotic fluid are considered nearly 100% accurate for the detection of large fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions usually can be detected only with the use of targeted FISH testing. Approximately 3% of amniotic fluid specimens analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and other environmental factors ( ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis prior to performing the amniocentesis. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values:
An interpretative report will be provided.


CHRCV 35251  
**Chromosome Analysis, Chorionic Villus Sampling**

**Clinical Information:** Although not used as widely as amniocentesis, the use of chorionic villus
sampling (CVS) for chromosome analysis is an important procedure for the prenatal diagnosis of chromosome abnormalities. CVS can be collected by either transcervical or transabdominal techniques. The medical indications for performing chromosome studies on CVS are similar to amniocentesis, and may include advanced maternal age, abnormal first-trimester screen, and family history of a chromosome abnormality. A chromosomal microarray (CMAP / Chromosomal Microarray, Prenatal) is recommended, rather than chromosomal analysis, to detect clinically relevant gains or losses of chromosomal material in pregnancies with one or more major structural abnormalities. Chromosomal microarray can also be considered, rather than chromosome analysis, for patients undergoing invasive prenatal diagnostic testing with a structurally normal fetus.

Useful For: Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy) and balanced rearrangements. This test is not appropriate as a first-tier test for detecting gains or losses of chromosomal material in pregnancies with 1 or more major structural abnormalities.

Interpretation: Cytogenetic studies on chorionic villus specimen (CVS) are considered more than 99% reliable for the detection of most fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions usually can be detected only with the use of targeted FISH testing. Approximately 3% of CSVs analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis before the procedure is performed, so that patients may make an informed decision about pursuing the procedure. Limitations: -False-chromosome mosaicism may occur due to artifact of culture -True mosaicism may be missed due to statistical sampling error -Presence of chromosome abnormalities in placental cells that do not occur in the cells of the fetus (confined placental mosaicism) -Subtle structural chromosome abnormalities can occasionally be missed. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values: An interpretive report will be provided.

environmental factors (ie, teratogen exposure). Chromosomal mosaicism may be missed due to statistical sampling error (rare) and subtle structural chromosome abnormalities can occasionally be missed.

**Useful For:** Diagnosis of congenital chromosome abnormalities, including aneuploidy, structural abnormalities, and balanced rearrangements

**Interpretation:** When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all abnormal results to the patient.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CHRHB 35308**

**Chromosome Analysis, Hematologic Disorders, Blood**

**Clinical Information:** Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and monitoring of treatment of many hematologic disorders. Whenever possible, it is best to do chromosome studies for neoplastic hematologic disorders on bone marrow. Bone marrow studies are more sensitive and the chances of finding metaphases are about 95%, compared with only a 60% chance for blood studies. When it is not possible to collect bone marrow, chromosome studies on blood may be useful. When blood cells are cultured in a medium without mitogens, the observation of any chromosomally abnormal clone may be consistent with a neoplastic process. Conventional chromosome studies of B-cell disorders are not always successful because B-lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B-cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia (CLL), and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Assisting in the classification and follow-up of certain malignant hematological disorders when bone marrow is not available

**Interpretation:** The presence of an abnormal clone usually indicates a malignant neoplastic process. The absence of an apparent abnormal clone in blood may result from a lack of circulating abnormal cells and not from an absence of disease. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality and, thus, not related to a malignant process. When this situation is suspected, follow-up with a medical genetics consultation is recommended.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. Dewald GW, Ketterling RP, Wyatt WA, Stupca PJ: Cytogenetic studies in

CHRBM

35245

Chromosome Analysis, Hematologic Disorders, Bone Marrow

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia; t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes. Conventional chromosome studies of B-cell disorders are not always successful because B lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia, and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival.

Useful For: Assisting in the diagnosis and classification of certain malignant hematological disorders Evaluating the prognosis in patients with certain malignant hematologic disorders Monitoring effects of treatment Monitoring patients in remission

Interpretation: To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: -Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, there may be a fluorescence in situ hybridization (FISH) study option that could be performed.

Reference Values:
An interpretative report will be provided.

**Clinical Information:** Clonal chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of pediatric hematologic malignancies. Whenever possible, it is best to do chromosome studies for neoplastic hematologic disorders on bone marrow. Bone marrow studies are more sensitive and the chances of finding metaphases are about 95%, compared with only a 60% chance for blood studies. When it is not possible to collect bone marrow, chromosome studies on blood may be useful. When blood cells are cultured in a medium without mitogens, the observation of any chromosomally abnormal clone may be consistent with a neoplastic process. Characteristic chromosome rearrangements and copy number patterns may help classify a pediatric hematologic malignancy. For example, t(1;19)(q23;p13.3) is typically observed in B-lymphoblastic leukemia/lymphoma (B-ALL) and t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; while t(7;14)(q35;q11.2) is associated with T-lymphoblastic leukemia/lymphoma. Confirmation of classic gene fusions associated with the above translocations together with evaluation for other recurrent abnormalities are available within the appropriate Children's Oncology Group (COG) fluorescence in situ hybridization (FISH) panels; COGBF / B-Lymphoblastic Leukemia/Lymphoma, Children's Oncology Group Enrollment Testing, FISH, Varies; COGTF / T-Cell Acute Lymphoblastic Leukemia (T-ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; and COGMF / Acute Myeloid Leukemia (AML), Children's Oncology Group Enrollment Testing, FISH, Varies. Some rearrangements identified by chromosomal analysis may be extremely rare but are known, recurrent entities for which the Mayo Clinic Genomics Laboratory has the most extensive catalogue of FISH testing to confirm the corollary gene fusions. Metaphase FISH confirmation of classic translocations which are cryptic and not visually detectable by chromosome analysis [ie, t(12;21)] associated with ETV6/RUNX1 fusion) is performed as required by COG and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intrachromosomal amplification of chromosome 21 (iAMP21).

**Useful For:** Evaluation of pediatric blood specimens for chromosomal abnormalities associated with hematologic malignancies for diagnostic and prognostic purposes in patients being considered for enrollment in Children’s Oncology Group clinical trials and research protocols

**Interpretation:** The presence of an abnormal clone usually indicates a malignant neoplastic process. The absence of an apparent abnormal clone in blood may result from a lack of circulating abnormal cells and not from an absence of disease. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality and, thus, not related to a malignant process. When this situation is suspected, follow-up with a medical genetics consultation is recommended.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
Clinical Information: Clonal chromosome abnormalities in bone marrow (or peripheral blood or tissue if bone marrow is not available) play a central role in the pathogenesis, diagnosis, and treatment monitoring of pediatric hematologic malignancies. Characteristic chromosome rearrangements and copy number patterns may help classify a pediatric hematologic malignancy. For example, t(1;19)(q23;p13.3) is typically observed in B-lymphoblastic leukemia/lymphoma (B-ALL) and t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; while t(7;14)(q35;q11.2) is associated with T-lymphoblastic leukemia/lymphoma. Confirmation of classic gene fusions associated with the above translocations together with evaluation for other recurrent abnormalities are available within the appropriate Children's Oncology Group (COG) fluorescence in situ hybridization (FISH) panels; COGBF / B-Lymphoblastic Leukemia/Lymphoma, Children's Oncology Group Enrollment Testing, FISH, Varies; COGT T-Cell Acute Lymphoblastic Leukemia (T-ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; and COGMF Acute Myeloid Leukemia (AML), Children's Oncology Group Enrollment Testing, FISH, Varies. Some rearrangements identified by chromosomal analysis may be extremely rare but are known recurrent entities for which the Mayo Clinic Genomics Laboratory has the most extensive catalogue of FISH testing to confirm the corollary gene fusions. Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome analysis (ie, t[12;21]) associated with ETV6/RUNX1 fusion) is performed as required by COG and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). If the expert cytogeneticist at Mayo Clinic reviewing a COGBM / Chromosome Analysis, Hematologic Disorders, Children's Oncology Group Enrollment Testing. Bone Marrow case feels microarray assay may be of benefit, the client will be contacted. For children in whom disease relapse or a secondary myeloid neoplasm is a concern and enrollment in a new COG protocol is being considered; COGBM for bone marrow chromosome analysis is appropriate.

Useful For: Evaluation of pediatric bone marrow specimens for chromosomal abnormalities associated with hematologic malignancies for diagnostic and prognostic purposes in patients being considered for enrollment in Children's Oncology Group clinical trials and research protocols

Interpretation: The following factors are important when interpreting the results: -Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a fluorescence in situ hybridization study option that could be performed.

Reference Values: An interpretative report will be provided.


CHFXH 64922 Chromosome Analysis, Hematologic Disorders, Fixed Cells

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis,
and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia, t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia, and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes.

**Useful For:**
Assisting in the diagnosis and classification of certain malignant hematological disorders
Evaluating the prognosis of patients with certain malignant hematologic disorders
Monitoring effects of treatment
Monitoring patients in remission

**Interpretation:**
To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results:
- Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition.
- The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis.
- On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended.
- On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a FISH study option that could be performed.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**Chromosome Analysis, Skin Biopsy**

**Clinical Information:**
Chromosomal abnormalities cause a wide range of disorders associated with birth defects and congenital diseases. Usually, the abnormalities can be demonstrated in peripheral blood, which is readily available. Chromosome analysis on skin fibroblasts may be indicated when the results from peripheral blood are inconclusive or in clinical circumstances such as suspected cases of chromosome mosaicism, confirmation of new chromosome disorders, or some dermatological disorders. Subtle structural chromosomal anomalies can occasionally be missed. Chromosomal mosaicism may be missed due to statistical sampling error (rare).

**Useful For:**
Diagnosis of mosaic congenital chromosome abnormalities, including mosaic aneuploidy and mosaic structural abnormalities
Subsequent chromosome analysis when results from peripheral blood are inconclusive

**Interpretation:**
When interpreting results, the following factors need to be considered:
- Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring.
- A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.
**Chronic Hepatitis (Unknown Type), Serum**

**Clinical Information:** Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic; others develop chronic liver disease including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of post-transfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. The following algorithms are available in Special Instructions: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Viral Hepatitis Serologic Profiles

**Useful For:** Diagnosis and evaluation of patients with symptoms of hepatitis with a duration more than 6 months Distinguishing between chronic hepatitis B and chronic hepatitis C

**Interpretation:** Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions. Chronic Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B viral (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic HBV infection. Hepatitis B core antibodies (anti-HBc Ab) appear shortly after the onset of symptoms of HBV infection and soon after the appearance of HBsAg. The IgM subclass usually falls to undetectable levels within 6 months, and the IgG subclass may remain for many years. Hepatitis B surface antibody (anti-HBs) usually appears with the resolution of hepatitis B virus infection after the disappearance of HBsAg. If HBsAg and anti-HBc (total antibody) are positive and patient's condition warrants, consider testing for hepatitis Be antigen (HBeAg), anti-HBe, hepatitis B virus DNA (HBV-DNA) or anti-hepatitis D virus (anti-HDV). Chronic Hepatitis C: Anti-HCV is almost always detectable by the late convalescent and chronic stage of infection. The serologic tests currently available do not differentiate between acute and chronic hepatitis C infections.

**Reference Values:**

HEPATITIS B SURFACE ANTIGEN

Negative

HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE

Hepatitis B Surface Antibody

Unvaccinated: negative

Vaccinated: positive

Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <5.0 mIU/mL
Vaccinated: > or =12.0 mIU/mL

HEPATITIS B CORE TOTAL ANTIBODIES
Negative

HEPATITIS C ANTIBODY
Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.


CHSBP 9023

Chronic Hepatitis Profile (Type B), Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion and sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic; others develop chronic liver disease including cirrhosis and hepatocellular carcinoma. The following are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles

Useful For: Evaluating patients with suspected or confirmed chronic hepatitis B Monitoring hepatitis B viral infectivity

Interpretation: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B viral (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either chronic carrier state or chronic liver disease. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. The
presence of hepatitis B antigen (HBeAg) correlates with infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and the presence of viral DNA polymerase in serum. Hepatitis B antibody (anti-HBe) positivity in a carrier is often associated with chronic asymptomatic infection. If the patient has a sudden exacerbation of disease, consider ordering hepatitis C virus antibody (anti-HCV) and hepatitis delta virus antibody (anti-HDV). If HBsAg converts to negative and patient's condition warrants, consider testing for anti-HBs. If HBsAg is positive, consider testing for anti-HDV. The following are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles

**Reference Values:**

**HEPATITIS B SURFACE ANTIGEN:**
Negative

**HEPATITIS Be ANTIGEN:**
Negative

**HEPATITIS Be ANTIBODY:**
Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

**CLLMV**

**Chronic Lymphocytic Leukemia (CLL) Monitoring Minimal Residual Disease (MRD) Detection, Varies**

**Clinical Information:** Chronic lymphocytic leukemia (CLL) is a low-grade, B-cell neoplasm that is the most common leukemia detected in the western world. It is a disease primarily of adults and may present as a lymphocytosis, be detected as part of a lymphadenopathy evaluation, or be found incidentally in an otherwise asymptomatic patient. The diagnosis of CLL is based on a combination of morphologic features showing primarily small lymphoid cells with coarse chromatin and scant cytoplasm and an immunophenotype of clonal B-cells with dim immunoglobulin, dim CD20, and coexpression of CD5 and CD23. New therapeutic approaches in CLL have been increasingly successful with some patients showing no or only very minimal residual disease (MRD) in their peripheral blood or bone marrow specimens following a therapeutic course. Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD is an important prognostic indicator in these patients.

**Useful For:** Confirming the presence or absence of minimal residual disease in patients with known chronic lymphocytic leukemia who are either postchemotherapy or post-bone marrow transplantation

**Interpretation:** An interpretive report for presence or absence of minimal residual disease (MRD) for chronic lymphocytic leukemia (CLL) is provided. Individuals without CLL should not have detectable clonal B cells in the peripheral blood or bone marrow. Patients who have detectable MRD by this assay are considered to have residual CLL disease.
**Reference Values:**
An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

**Clinical References:**
2. Varghese AM, Rawstron AC, Hillmen P: Eradicating minimal residual disease in chronic lymphocytic leukemia: should this be the goal of treatment? Curr Hematol Malig Rep 2010;5:35-44

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**CLLDF 610713**

**Chronic Lymphocytic Leukemia (CLL), Diagnostic FISH, Varies**

**Clinical Information:**
Chronic lymphocytic leukemia (CLL) is the most common leukemia in North America. The most common cytogenetic abnormalities in CLL involve chromosomes 6, 11, 12, 13 and 17. These are detected and quantified using the CLL fluorescence in situ hybridization (FISH) panel. Use of CpG-oligonucleotide mitogen will identify an abnormal CLL karyotype in at least 80% of cases. This mitogen is added to cultures when chromosome analysis is ordered and the reason for referral is a B-cell disorder (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow and CHRHB / Chromosome Analysis, Hematologic Disorders, Blood). This FISH test detects an abnormal clone in approximately 70% of patients with indolent disease and in greater than 80% of patients who require treatment. At least 5% of patients referred for CLL FISH testing have translocations involving the IGH locus. Fusion of IGH with CCND1 is associated with t(11;14)(q13;q32), and fusion of IGH with BCL3 is associated with t(14;19)(q32;q13.3). Patients with t(11;14) usually have the leukemic phase of mantle cell lymphoma. Patients with t(14;19) may have an atypical form of B-CLL or the leukemic phase of a lymphoma. The prognostic associations for chromosome abnormalities detected by this FISH assay are, from best to worst: 13q-, normal, +12, 6q-, 11q- and 17p-.

**Useful For:**
Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with chronic lymphocytic leukemia (CLL) Identifying and tracking known chromosome abnormalities in patients with CLL and tracking response to therapy Distinguishing patients with 11;14 translocations who have leukemic phase of mantle cell lymphoma from patients who have CLL Detecting patients with atypical CLL or other forms of lymphoma associated with translocations between IGH and BCL3

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Chronic Lymphocytic Leukemia (CLL), Specified FISH, Varies

**Clinical Information:** Chronic lymphocytic leukemia (CLL) is the most common leukemia in North America. The most common cytogenetic abnormalities in CLL involve chromosomes 6, 11, 12, 13, and 17. These are detected and quantified using the CLL fluorescence in situ hybridization (FISH) panel. Use of CpG-oligonucleotide mitogen will identify an abnormal CLL karyotype in at least 80% of cases. This mitogen is added to cultures when chromosome analysis is ordered and the reason for testing is a B-cell disorder (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow and CHRRH / Chromosome Analysis, Hematologic Disorders, Blood). This FISH test detects an abnormal clone in approximately 70% of patients with indolent disease and greater than 80% of patients who require treatment. At least 5% of patients referred for CLL FISH testing have translocations involving the IGH locus. Fusion of IGH with CCND1 is associated with t(11;14)(q13;q32), and fusion of IGH with BCL3 is associated with t(14;19)(q32;q13.3). Patients with t(11;14) usually have the leukemic phase of mantle cell lymphoma. Patients with t(14;19) may have an atypical form of B-CLL or the leukemic phase of a lymphoma. The prognostic associations for chromosome abnormalities detected by this FISH assay are, from best to worst: 13q-, normal, +12, 6q-, 11q-, and 17p-.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with chronic lymphocytic leukemia (CLL) Identifying and tracking known chromosome abnormalities in patients with CLL and tracking response to therapy Distinguishing patients with 11;14 translocations who have leukemic phase of mantle cell lymphoma from patients who have CLL Detecting patients with atypical CLL or other forms of lymphoma associated with translocations between IGH and BCL3

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

**Reference Values:** An interpretive report will be provided.


Chub Mackerel, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to chub mackerel. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Chyluria Screen, Random, Urine**

**Clinical Information:** Chyluria is a medical condition in which chyle is present in the urine. Chyle is a milky substance composed of lymphatic fluid and chylomicrons formed in the small intestine during the digestion of fatty foods. Chyluria is most prevalent in tropical areas where it is caused by parasitic (Wuchereria bancrofti) infections spread by mosquitoes. Parasitic chyluria is so rare as to be nonexistent in the continental United States. Nonparasitic chyluria causes include traumatic lesions, tumors, lymphangioma, pregnancy, and granulomatous infections.

**Useful For:** Aids in the diagnosis of chyluria (galacturia)

**Interpretation:** This assay provides information regarding the fat content in urine fluid. Urinary cholesterol and triglyceride values are normally less than 10 mg/dL. High triglycerides in urine may indicate chyluria.

**Reference Values:**

No lipoproteins present

Chymotrypsin, Stool
Reference Values:
2.3 Æ­– 51.4 U/g

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

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

Useful For: Establishing a diagnosis of an allergy to cinnamon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35–0.69 Equivocal
2 0.70–3.49 Positive
3 3.50–17.4 Positive
4 17.5–49.9 Strongly positive
5 50.0–99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.
**Circulating Immune Complexes (CIC)**

**Interpretation:** Circulating immune complexes (CICs) are detectable in a variety of systemic disorders such as rheumatological, autoimmune, allergic diseases; viral, bacterial infections and malignancies. Although detection of CICs is neither essential nor specific for any disease, anti-C1q assay is likely to provide information regarding disease activity in lupus nephritis.

**Reference Values:**
- **Negative** <20 EU/mL
- **Borderline/Equivocal** 20–25 EU/mL
- **Positive** >25 EU/mL

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**Citalopram, Serum**

**Clinical Information:** Citalopram (Celexa) and S-citalopram (escitalopram, Lexapro) are approved for treatment of depression. Celexa is a racemic mixture containing equal amounts of R- and S-enantiomer. Metabolites of citalopram (N-desmethylcitalopram) are less active than citalopram and do not accumulate in serum to clinically significant concentration. Citalopram metabolism is carried out by cytochrome P450 (CYP) 2C19 and 3A4-5. CYP 2D6 may play a minor role in citalopram metabolism. Citalopram is known to reduce CYP 2D6 activity. Citalopram clearance is significantly affected by reduced hepatic function, but only slightly by reduced renal function. A typical Celexa dose administered to an adult is 40-mg per day. A typical Lexapro dose is 20-mg per day. Citalopram is 80% protein bound, and the apparent volume of distribution is 12 L/Kg. Bioavailability is 80% and protein binding is 56% for either form of the drug. Time to peak serum concentration is 4 hours, and the elimination half-life is 35 hours. Half-life is increased in the elderly. Dosage reductions may be necessary for patients who are elderly or have reduced hepatic function.

**Useful For:** Monitoring citalopram therapy Identifying noncompliance, although regular blood level monitoring is not indicated in most patients Identifying states of altered drug metabolism when used in conjunction with CYP2C19 and CYP3A4-5 genotyping

**Interpretation:** Steady-state serum concentrations associated with optimal response to citalopram are in the range of 50 to 100 ng/mL when the patient is administered the R,S-enantiomeric mixture (Celexa). The most common toxicities associated with excessive serum concentration are fatigue, impotence, insomnia, and anticholinergic effects. The toxic range for citalopram is greater than 220 ng/mL.

**Reference Values:**
- Citalopram: 50-110 ng/mL
- Escitalopram: 15-80 ng/mL

**Clinical References:**

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**Citrate Concentration, Random, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal
tubular pH or intracellular pH may decrease citrate (e.g., metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

**Interpretation:** A low citrate value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low citrate levels suggest investigation for the possible diagnosis of metabolic acidosis (e.g., renal tubular acidosis). For children ages 5 to 18, a ratio of less than 0.176 mg citrate/mg creatinine is below the 5% reference range and considered low.(1)

**Reference Values:**
Only orderable as part of a profile. For more information see CITRA / Citrate Excretion, Random, Urine.

No established reference values


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**Citrate Excretion, 24 Hour, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (e.g., metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate promotes kidney stone formation and growth, and is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

**Interpretation:** Any value less than the mean for 24 hours represents a potential risk for kidney stone formation and growth. Patients with low urinary citrate and new or growing stone formation, may benefit from adjustments in therapy known to increase urinary citrate excretion. (See Clinical Information) Very low levels (<150 mg/24 hours) suggest investigation is needed for the possible diagnosis of metabolic acidosis (e.g., renal tubular acidosis).

**Reference Values:**
0-19 years: not established
20 years: 150-1,191 mg/24 hours
21 years: 157-1,191 mg/24 hours
22 years: 164-1,191 mg/24 hours
23 years: 171-1,191 mg/24 hours
24 years: 178-1,191 mg/24 hours
25 years: 186-1,191 mg/24 hours
26 years: 193-1,191 mg/24 hours
27 years: 200-1,191 mg/24 hours
28 years: 207-1,191 mg/24 hours
29 years: 214-1,191 mg/24 hours
30 years: 221-1,191 mg/24 hours
31 years: 228-1,191 mg/24 hours
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<td>434-1,191</td>
</tr>
<tr>
<td>&gt;60</td>
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</tbody>
</table>


**CITRA 606715**

**Citrate Excretion, Random, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Diagnosing risk factors for patients with calcium kidney stones using random urine specimens Monitoring results of therapy in patients with kidney stones or renal tubular acidosis

**Interpretation:** A low value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low citrate levels suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis). For children ages 5 to 18, a ratio of less than 0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

**Reference Values:**
No established reference values.

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**Citrate/Creatinine Ratio, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (e.g., metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Calculating the citrate concentration per creatinine Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

**Interpretation:** A low citrate value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low citrate levels suggest investigation for the possible diagnosis of metabolic acidosis (e.g., renal tubular acidosis). For children ages 5 to 18, a ratio of less than 0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

**Reference Values:** Only orderable as part of a profile. For more information see CITRA / Citrate Excretion, Random, Urine.

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**Cladosporium, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Cladosporium Defining the allergen responsible
for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Clam, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to clam Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</table>
### CLAUD 70403

#### Claudin-1 Immunostain, Technical Component Only

**Clinical Information:** Claudin proteins are a family of tight junction-associated proteins that prevent leakage of ions, water, etc between cells. Differential expression of claudin proteins is seen in various epithelial cell types. Strong expression of claudin-1 is seen on squamous epithelial cells of the skin. Claudin-1 may have reduced expression in invasive versus benign breast lesions. In the diagnostic setting, 30% to 50% of soft tissue and intramucosal intestinal perineuriomas are positive for claudin-1. Gastric intestinal-type adenocarcinoma shows more frequent claudin-1 expression than diffuse gastric carcinomas.

**Useful For:** Identification of a number of different soft tissue and epithelial neoplasms

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### CLDN4 607334

#### Claudin-4 Immunostain, Technical Component Only

**Clinical Information:** Claudin-4 is a component of tight junction strands and is expressed on the membrane of cells of epithelial origin. Claudin-4 has been shown to distinguish carcinoma from mesothelioma and carcinoma from sarcoma.

**Useful For:** Distinguishing carcinoma from mesothelioma and sarcoma

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**FCLCN 75262**

**CLCN1 DNA Sequencing Test**

**Reference Values:**
A final report will be attached in MayoAccess.

**CLOBZ 65483**

**Clobazam and Metabolite, Serum**

**Clinical Information:** Clobazam is a broad spectrum, antiepileptic drug used for various types of seizures, Lennox-Gastaut syndrome (a type of childhood onset epilepsy), and migraine prophylaxis. Clobazam blocks voltage-dependent sodium channels, potentiates gamma-aminobutyric acid (GABA) activity at some of the GABA receptors, and inhibits potentiation of the glutamate receptor and carbonic anhydrase enzyme, all which contribute to its antiepileptic and antimigraine efficacy. In general, clobazam shows favorable pharmacokinetics with good absorption (1-4 hours for the immediate-release formulation), low protein binding, and minimal hepatic metabolism. Elimination is predominantly renal, and it is excreted unchanged in the urine with an elimination half-life of approximately 21 hours. As with other anticonvulsant drugs eliminated by the renal system, patients with impaired renal function exhibit decreased clobazam clearance and a prolonged elimination half-life. Serum concentrations of other anticonvulsant drugs are not significantly affected by the concurrent administration of clobazam, with the exception of patients on phenytoin whose serum concentrations can increase after the addition of clobazam. Other drug-drug interactions include the coadministration of phenobarbital, phenytoin, or carbamazepine, which can result in decreased clobazam concentrations. In addition, concurrent use of posaconazole and clobazam may result in the elevation of clobazam serum concentrations. Therefore, changes in cotherapy with these medications (phenytoin, carbamazepine, posaconazole, or phenobarbital) may require dose adjustment of clobazam and therapeutic drug monitoring can be helpful. The most common adverse drug effects associated with clobazam include: weight loss, loss of appetite, somnolence, dizziness, coordination problems, memory impairment, and paresthesia.

**Useful For:** Monitoring clobazam therapy

**Interpretation:** The results of this test should be interpreted in conjunction with the patient's physical signs, symptoms, and other laboratory test results. Most individuals display optimal response to clobazam when serum levels of clobazam are between 30 and 300 ng/mL and N-desmethylclobazam are between 300 and 3000 ng/mL. Risk of toxicity is increased when clobazam levels are above 500 ng/mL or N-desmethyloclobazam levels are above 5000 ng/mL. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range, thus, interpretation should include clinical evaluation.

**Reference Values:**

**CLOBAZAM**
Therapeutic Range: 30-300 ng/mL

**NORCLOBAZAM**
Therapeutic Range: 300-3,000 ng/mL

**Clinical References:** 1. Hiemke C, Bergemann N, Clement HW, et al: Consensus guidelines for

Clomipramine, Serum

Clinical Information: Clomipramine (chlorimipramine, Anafranil) is a tricyclic antidepressant drug used primarily to treat obsessive-compulsive disorder. Clomipramine is also used to treat panic disorder and treatment-resistant depression. Clomipramine preferentially blocks synaptic reuptake of serotonin; its pharmacologically active metabolite, norclomipramine (desmethylchlorimipramine) preferentially blocks synaptic reuptake of norepinephrine. Clomipramine undergoes significant first-pass hepatic metabolism (up to 50%), which probably explains the high degree of interindividual variability observed between administered dose and steady-state serum concentrations of the drug and its metabolite. The serum ratio of clomipramine to norclomipramine is typically 1:2-2.5. The elimination half-lives of clomipramine and norclomipramine are 19 to 37 hours and 54 to 77 hours, respectively. When a patient is started on clomipramine or following an alteration in the dose, 1 to 2 weeks are required to achieve a steady-state condition. Anticholinergic side effects (ie, dry mouth, excessive sweating, blurred vision, urinary retention, constipation) frequently accompany treatment. Other side effects may include tremor, nausea, orthostatic hypotension, dizziness, sexual dysfunction, and sleep disturbances. Signs and symptoms following overdose are similar to other tricyclic antidepressant drugs: cardiac toxicity (eg, tachycardia, arrhythmia, impaired conduction, congestive heart failure) is the major concern.

Useful For: Determining whether a poor therapeutic response is attributable to noncompliance

Monitoring serum concentration of clomipramine and norclomipramine to assist in optimizing the administered dose

Interpretation: Studies investigating the relationship between serum concentrations of clomipramine and norclomipramine and therapeutic response have yielded conflicting results. However, the probability of therapeutic failure seems to increase if the sum of the clomipramine and norclomipramine serum concentrations is <230 ng/mL. Summed serum concentrations of clomipramine and norclomipramine that exceed 450 ng/mL seem to result in no additional enhancement in therapeutic response and may predispose the patient to greater risk of adverse side effects. A toxic range has not been well established at this time.

Reference Values:
CLOMIPRAMINE AND NORCLOMIPRAMINE
Therapeutic concentration: 230-450 ng/mL

Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


Clonazepam and 7-Aminoclonazepam, Serum

Clinical Information: Clonazepam (5-[2-chlorophenyl]-2,3-dihydro-7-nitro-1,4-benzodiazepin-2-one), a benzodiazepine is useful alone or as an adjunct in the treatment of certain seizures. In addition, it may be useful in patients with panic disorder and restless legs syndrome. Clonazepam has no definite antiseizure and antipanic mechanism of action, although it is believed to be
related to its capacity to enhance gamma-aminobutyric acid (GABA) activity, which is the major inhibitory neurotransmitter in the central nervous system. It is able to suppress the spike and wave discharges in absence seizures and decreases the frequency, duration, amplitude, and spread of discharge in minor motor seizures. Clonazepam is highly protein bound (approximately 85%). It is extensively metabolized by hepatic cytochrome P450, family 3, subfamily A (CYP3A) to inactive metabolites and has a half-life of 30 to 40 hours.

**Useful For:** Assessing patient compliance Monitoring for appropriate therapeutic level Assessing clonazepam toxicity

**Interpretation:** The therapeutic range varies depending on the indication. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range, and thus, interpretation should include clinical evaluation. The possibility of toxicity is increased when levels exceed 100 ng/mL.

**Reference Values:**
- Clonazepam
  - Anticonvulsant: 20-70 ng/mL
  - Anxiolytic: 4-80 ng/mL
  - Some individuals may show therapeutic response outside of these ranges or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation.
  - Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


**Clonidine (Catapres)**

**Reference Values:**
- Reference Range: 1.00 - 2.00 ng/mL

  - Sedation has been associated with serum clonidine concentrations greater than 1.5 ng/mL.
  - Toxic concentration has not been established.

**Clostridioides difficile Culture, Varies**

**Clinical Information:** Clostridioides difficile (formerly Clostridium difficile) can cause diarrhea and may cause pseudomembranous colitis. Overgrowth of toxin-producing C difficile in the colon leads to the production of toxins A and/or B by the organism and consequent diarrhea. C difficile infection should be suspected in patients with symptoms of diarrhea with risk factors such as current or recent use of antibiotics, a history of C difficile infection, current or recent hospitalization or placement in a nursing home or long-term care facility, age older than 65 years, gastric acid suppression, etc. C difficile infection is the most common cause of diarrhea in hospitalized patients and may lead to serious complications, including sepsis, bowel perforation, and increased overall mortality (especially in older patients). The incidence of C difficile infection has risen in the community and in healthcare settings. While culture is not the preferred means to diagnose C difficile-associated diarrhea, culture for C difficile provides an isolate suitable for antimicrobial susceptibility testing. Note that this test does not differentiate between toxin-producing and nontoxigenic strains of C difficile.

**Useful For:** Providing an isolate suitable for antimicrobial susceptibility testing.

**Interpretation:** A positive result indicates the presence of viable Clostridioides difficile in feces. A positive culture may be found with asymptomatic C difficile colonization with a toxin-producing or non-toxin-producing strain, or with C difficile-associated diarrhea. A negative result indicates the absence of C difficile growth in culture. Isolation of C difficile does not differentiate between
toxin-producing and non-toxin-producing strains.

Reference Values:
No growth after 1 day of incubation.


Clostridioides difficile Toxin, Molecular Detection, PCR, Feces

Clinical Information: Clostridioides difficile (formerly Clostridium difficile) is the cause of C difficile-associated diarrhea (CDAD), an antibiotic-associated diarrhea, and pseudomembranous colitis (PMC). In these disorders bacterial overgrowth of C difficile develops in the colon, typically as a consequence of antibiotic usage. Clindamycin and broad-spectrum cephalosporins have most frequently been associated with CDAD and PMC, but almost all antimicrobials may be responsible. Disease is related to production of toxin A and B. Treatment typically involves withdrawal of the associated antimicrobials and, if symptoms persist, orally administered and intraluminally active metronidazole, vancomycin, or fidaxomicin. Intravenous metronidazole may be used if an oral agent cannot be administered. In recent years, a more severe form of CDAD with increased morbidity and mortality has been recognized as being caused by an epidemic toxin-hyperproducing strain of C difficile (NAP1 strain). Many toxin-hyperproducing isolates also contain the binary toxin gene and are resistant to quinolones. This test does not differentiate between toxin-hyperproducing and nontoxin-hyperproducing strains. Traditionally, diagnosis relied upon 1) clinical and epidemiologic features, 2) culture, which is labor intensive and time consuming, 3) cytotoxicity assays, which are also labor intensive and time consuming, and 4) toxin detection immunoassays, which are insensitive. The described polymerase chain reaction assay detects the regulatory gene (tdcC) responsible for production of toxins A and B. This test is used for rapid diagnosis of CDAD and PMC enabling prompt treatment that may reduce hospital stays for inpatients with CDAD.

Useful For: Rapid diagnosis of Clostridioides difficile-associated diarrhea (CDAD) and pseudomembranous colitis (PMC)

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of the gene regulating toxin production (tdcC) indicates the presence of Clostridioides difficile and toxin A and/or B. A negative result indicates the absence of detectable C difficile tdcC DNA, but does not rule-out C difficile infection and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of C difficile DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

CLOV
82490

Clove, IgE, Serum

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

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

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
who are at risk for recurrent suicidal behavior and who have encountered nonresponse or adverse, intolerable extrapyramidal side effects with more classical antipsychotics (chlorpromazine, haloperidol). Although clozapine was developed about 30 years ago and the initial results were promising, the development of several fatal cases of agranulocytosis resulted in the discontinued use of this agent. Seizures, an increased risk of fatal myocarditis, and orthostatic hypotension have also been associated with the use of clozapine. The use of clozapine has regained interest for several reasons. Patients who did not respond to treatment with other antipsychotics improved when clozapine was administered. Also, the agranulocytosis that occurs in approximately 1% to 2% of patients can be controlled with close hematologic monitoring. However, because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should only be used in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse reactions from those drugs. Treatment is usually started with dosages of 25 to 75 mg/day with a gradual increase to reach a final dose of 300 to 450 mg/day within approximately 2 weeks of the initiation of treatment. Once the desired effect is achieved, the dose may be gradually decreased to keep the patient on the lowest possible effective dose. Patients being treated with clozapine should be closely monitored during treatment for adverse reactions. Treatment must include monitoring of white blood cell count and absolute neutrophil count. Clozapine treatment should be discontinued in patients failing to show an acceptable clinical response. In addition, in patients exhibiting beneficial clinical responses, the need for continuing treatment should be periodically reevaluated. Clozapine is metabolized to desmethylated and N-oxide derivatives. The desmethyl metabolite (norclozapine) has only limited activity, and N-oxide metabolite is inactive.

**Useful For:** Monitoring patient compliance An aid to achieving desired plasma levels

**Interpretation:** The effectiveness of clozapine treatment should be based on clinical response and treatment should be discontinued in patients failing to show an acceptable clinical response.

**Reference Values:**

**CLOZAPINE**  
Therapeutic range: 350-600 ng/mL

**NORCLOZAPINE**  
Therapeutic range: Not well established

**CLOZAPINE + NORCLOZAPINE**  
Therapeutic range: Not well established


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**Clusterin Immunostain, Technical Component Only**

**Clinical Information:** In lymph nodes, tonsils, and spleen, clusterin stains the follicular dendritic cell meshworks. B cells, T cells, and histiocytes are negative. Clusterin is often positive in the tumor cells of systemic anaplastic large-cell lymphoma and is usually negative in Reed Sternberg cells in classical Hodgkin lymphoma. It is a sensitive marker for follicular dendritic cell sarcomas.
Useful For: A marker of follicular dendritic cells

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CMET
70405

cMET Immunostain, Technical Component Only

Clinical Information: c-Met, a cell surface receptor tyrosine kinase, regulates cellular proliferation, migration, and differentiation during development. Increased expression of c-Met has been shown to correlate with poor prognosis in nonsmall cell carcinomas of the lung.

Useful For: Identification of normal and neoplastic c-Met expressing cells

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


CMV by PCR
91734

Reference Values:
Not detected = Negative, no virus detected
Detected = Positive, virus detected
<1000 copies/mL = Positive. Virus detected below 1000 copies/mL
1000 copies/mL to 1,000,000 copies/mL = Positive
>1,000,000 copies/mL = Positive. Virus detected above maximum quantitative range.

This test employs real-time PCR amplification of a Cytomegalovirus-specific conserved genetic target. A “Not detected” A “~A “Not detected“
result for this assay does not exclude Cytomegalovirus involvement in a disease process.

**FDMZ 57859**

**CNBP DNA Test (DM2)**

**Clinical Information:** Detects CCTG repeat expansions in the Zinc Finger Protein 9 (ZNF9) gene. Typical Presentation: Individuals with a range of symptoms from cataracts to significant muscle wasting, cardiac complications, ptosis and myotonia.

**Reference Values:**
A final report will be attached in MayoAccess.

**CDS1 65565**

**CNS Demyelinating Disease Evaluation, Serum**

**Clinical Information:** Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease (IDD) that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD).(1-3) Brain lesions are observed in more than 60% of patients with NMOSD and approximately 10% will be MS-like.(4) Children tend to have greater brain involvement than adults, and brain lesions are more symptomatic than is typical for adult patients.(3) The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Some patients may present with acute disseminated encephalomyelitis (ADEM). Many patients with NMOSD are misdiagnosed as having MS. More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Â Approximately 80% of patients with NMO are seropositive for aquaporin-4 (AQP4)-IgG.(5-7) In the remaining 20% of patients, myelin oligodendrocyte glycoprotein (MOG)-IgG is detected in up to a third.(8) The pathogenic target for the remaining patients remains unknown. Detection of MOG-IgG is diagnostic of central nervous system (CNS) inflammatory demyelination, where the clinical phenotype (NMOSD, optic neuritis, transverse myelitis, ADEM) may be similar, but the immunopathology (astrocytopathy vs oligodendrogliopathy) and clinical outcome (worse vs better) is different.(9) Detection of MOG-IgG also predicts relapse.(10) More importantly, however, is that MOG-IgG seropositive IDDs are distinct from MS and treated differently.(8, 9) Treatments for IDDs seropositive for MOG-IgG include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Disease modifying agents, treatments promoted for MS, have been reported to exacerbate MOG-IgG1 seropositive IDDS. Therefore, early diagnosis and initiation of appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. In 2015, Waters and colleagues (11) from Oxford University established a novel cell based assay for the measurement of IgG1 MOG antibodies based on previous findings that MOG antibodies are almost exclusively of the IgG1 subclass. They showed that their MOG-IgG1 flow cytometry assay eliminated false-positives without losing true-positives with low titers. The detection of MOG-IgG1 allowed non MS demyelinating diseases (ADEM, AQP4-IgG negative neuromyelitis optica spectrum disorder: including ON,TM) to be distinguished from MS.(12) Â Using a similar assay to our MOG-IgG1 flow cytometry assay, Wingerchuk et al demonstrated high specificity of their MOG-IgG1 assay in which 49 patients with MS, 13 healthy control sera, and 37 AQP4-seropositive serum samples were all negative at a dilution of 1:20. Of 58 patients fulfilling 2006 Wingerchuk criteria for NMO, 21 (36%) tested negative for AQP4-IgG MOG-IgG1 was detected by cell based assay in 8 (38%) of these cases. (13) Â Testing of 1,109 consecutive sera sent for AQP4-IgG testing,(11) revealed 40 AQP4-IgG and 65 MOG-IgG1 positive cases. None were positive for both. The clinical diagnoses obtained in 33 MOG-IgG1 positive patients included 4 NMO, 1 ADEM and 11 optic neuritis (n = 11). All 7 patients with probable MS were MOG-IgG1 negative. This study provides Class II evidence that the presence of serum MOG-IgG1 distinguishes non-MS central nervous system (CNS) demyelinating disorders from MS (sensitivity 24%, 95% confidence interval [CI] 9%-45%; specificity 100%, 95% CI 88%-100%). Â The assay validated here, was developed using the MOG construct provided by Dr Waters(11) and the validation was based on a blinded comparison with the Oxford assay. Comparison was also made with the Euroimmun fixed cell-based kit assay.(14) Â A recent longitudinal analysis with 2 year follow-up suggested that persistence of MOG-IgG is associated with relapses thus warranting relapse preventing.(10) Detection of MOG-IgG1 allows distinction from MS and is generally indicative of a
relapsing disease, mandating initiation of immunosuppression, even after the first attack in some, thereby reducing attack frequency and disability in the future.

**Useful For:** Diagnosis of inflammatory demyelinating diseases (IDDs) with similar phenotype to neuromyelitis optica spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis Diagnosis of autoimmune myelin oligodendrocyte glycoprotein (MOG)-opathy Diagnosis of neuromyelitis optica (NMO) Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease Diagnosis of ADEM Prediction of a relapsing disease course

**Interpretation:** A positive value for aquaporin-4 (AQP4)-IgG is consistent with an autoimmune astrocytopathy/neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months if NMOSD is suspected. A positive value for myelin oligodendrocyte glycoprotein (MOG)-IgG is consistent with an neuromyelitis optica (NMO)-like phenotype, and in the setting of acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and transverse myelitis (TM) indicates an autoimmune oligodendroglialopathy with potential for relapsing course. Identification of MOG-IgG allows distinction from multiple sclerosis (MS) and may justify initiation of appropriate immunosuppressive therapy (not MS disease-modifying agents) at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months as persistence of MOG-IgG seropositivity predicts a relapsing course. Detection of both antibodies is rare and unusual. AQP4-IgG and MOG-IgG are not found in MS or healthy subjects.

**Reference Values:**

MOG FACS, S
- Negative
  Reference values apply to all ages.

NMO/AQP4 FACS, S
- Negative
  Reference values apply to all ages.

**Clinical References:**
Coagulation Factor II Activity Assay, Plasma

Clinical Information: Factor II (prothrombin) is a vitamin K-dependent serine protease synthesized in liver. It participates in the final common pathway of coagulation, as the substrate for the prothrombinase enzyme complex. Prothrombin is the precursor of thrombin (IIa), which converts fibrinogen to fibrin. Plasma biological half-life is about 3 days. Deficiency of factor II may cause prolonged prothrombin time and activated partial thromboplastin time. Deficiency may result in a bleeding diathesis.

Useful For: Diagnosing a congenital deficiency (rare) of coagulation factor II Evaluating acquired deficiencies associated with liver disease or vitamin K deficiency, oral anticoagulant therapy, and antibody-induced deficiencies (eg, in association with lupus-like anticoagulant) Determining warfarin treatment stabilization in patients with nonspecific inhibitors (ie, lupus anticoagulant) Determining degree of anticoagulation with warfarin to correlate with level of protein S Investigation of prolonged prothrombin time or activated partial thromboplastin time

Interpretation: Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor II activity. Patients that are homozygous generally have levels of less than 25% activity. Patients that are heterozygous generally have levels of less than 50% activity. Normal newborn infants may have levels of 25% to 50%.

Reference Values: Adults: 75-145% Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

Reference: See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.


Coagulation Factor IX Activity Assay, Plasma

Clinical Information: Factor IX is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital deficiency inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) characterized by hemarthroses, deep tissue bleeding, excessive bleeding with trauma and ecchymoses. Acquired deficiency associated with liver disease, vitamin K deficiency, warfarin therapy and inhibitors (rare).

Useful For: Diagnosing deficiencies, particularly hemophilia B (Christmas disease) Assessing the impact of liver disease on hemostasis Investigation of a prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is more common than congenital. Mild hemophilia B: 5% to 50% activity Moderate hemophilia B: 1% to 5% activity Severe hemophilia B: <1% activity

Reference Values: < or =6 months: Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which may not reach adult levels for > or =180 days postnatal.* (Literature derived) >6 months: 65-140%

Reference: See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

Clinical References: 1. Barrowcliffe TW, Raut S, Sands D, Hubbard AR: Coagulation and
Coagulation Factor V Activity Assay, Plasma

**Clinical Information:** Factor V is a vitamin K-independent protein synthesized in the liver and in other tissues (endothelium, megakaryocytes/platelets). In its thrombin-activated form (factor Va), it serves as an essential cofactor in the prothrombinase enzyme complex, which converts prothrombin to thrombin (the prothrombinase complex consists of the enzyme, activated factor X, factor Va cofactor, a phospholipid surface, and calcium). Deficiency of factor V may cause prolonged prothrombin time and activated partial thromboplastin time and may result in a bleeding diathesis. Plasma biological half-life varies from 12 to 36 hours. Platelets contain 20% to 25% of the factor V in blood. Factor V (also known as labile factor) is highly susceptible to proteolytic inactivation, with the potential for spuriously decreased assay results.

**Useful For:** Diagnosing congenital deficiencies (rare) of coagulation factor V Evaluating acquired deficiencies associated with liver disease, factor V inhibitors, myeloproliferative disorders, and intravascular coagulation and fibrinolysis Investigation of prolonged prothrombin time or activated partial thromboplastin time

**Interpretation:** Acquired deficiencies are much more common than congenital. Patients that are congenitally deficient homozygous generally have activity levels less than or equal to 10% to 20%. Patients that are congenitally deficient heterozygous generally have activity levels less than or equal to 50%. Congenital deficiency may occur in combined association with factor VIII deficiency.

**Reference Values:**

- >1 month: 70%-165%
- <1 month: Normal, full-term and premature newborn infants may have mildly decreased levels (> or =30% to 35%) which reach adult levels within 21 days postnatal.

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Clinical References:**


Coagulation Factor VII Activity Assay, Plasma

**Clinical Information:** Factor VII is a vitamin K-dependent serine protease synthesized in the liver. It is a component of the extrinsic coagulation scheme, measured by the prothrombin time. Plasma biological half-life is about 3 to 6 hours. Deficiency may result in a bleeding diathesis.

**Useful For:** Diagnosing congenital deficiency of coagulation factor VII Evaluating acquired deficiencies associated with liver disease, oral anticoagulant therapy, and vitamin K deficiency Determining degree of anticoagulation with warfarin to correlate with level of protein C Investigation of a prolonged prothrombin time

**Interpretation:** Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor VII activity. Patients that are homozygous have levels usually less than 20% activity. Patients that are heterozygous generally have levels of less than or =50% activity. Newborn infants usually have...
levels greater than or =25%.

**Reference Values:**

**Adults:** 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.


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**Coagulation Factor VIII Activity Assay, Plasma**

**Clinical Information:** Factor VIII is synthesized in the liver and, perhaps, in other tissues. It is a coagulation cofactor that circulates bound to von Willebrand factor and is part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours). Congenital factor VIII deficiency is the cause of hemophilia A, which has an incidence of 1 in 10,000 and is inherited in a recessive sex-linked manner on the X chromosome. Severe deficiency (<1%) characteristically demonstrates as hemarthrosis, deep-tissue bleeding, excessive bleeding with trauma, and ecchymoses. Factor VIII may be decreased in von Willebrand disease. Acquired deficiency states also occur. Antibodies specific for factor VIII are the most commonly occurring specific inhibitors of coagulation factors and can produce serious bleeding disorders (acquired hemophilia). Spuriously decreased results may occur as factor VIII is highly susceptible to proteolytic inactivation.

**Useful For:** Diagnosing hemophilia A Diagnosing von Willebrand disease when measured with the von Willebrand factor (VWF) antigen and VWF activity. Diagnosing acquired deficiency states Investigation of prolonged activated partial thromboplastin time Monitoring infusions of factor VIII replacement during interventional procedures and prophylactic infusions. This test is not useful for inferring carrier status in suspected female carriers of hemophilia A, unless it is 50% of normal (<28% activity in adults).

**Interpretation:** Mild hemophilia A: 5% to 50% activity Moderate hemophilia A: 1% to 5% activity Severe hemophilia A: <1% activity Congenital deficiency may also occur in combined association with factor V deficiency. Liver disease usually causes an increase of factor VIII activity. Acquired deficiencies of factor VIII have been associated with myeloproliferative or lymphoproliferative disorders (acquired von Willebrand disease: VWD), inhibitors of factor VIII (autoantibodies, postpartum conditions, etc), and intravascular coagulation and fibrinolysis. Levels may be decreased with von Willebrand factor in VWD.

**Reference Values:**

**Adults:** 55-200%

Normal, full-term newborn infants or healthy premature infants typically have levels greater than or equal to 400%.*

*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

Coagulation Factor VIII Inhibitor Screen, Plasma

**Clinical Information:** Specific factor inhibitors are antibodies that are found most often in response to the use of factor VIII concentrate by patients congenitally deficient in factor VIII (hemophilia A). Factor VIII inhibitors can also develop in non-hemophilic patients (not previously factor VIII deficient), most commonly in the following: the elderly, postpartum patients, and patients with autoimmune disease. Testing will include coagulation factor VIII activity assay with dilutions to evaluate assay inhibition, and if the factor VIII assay activity is decreased, an inhibitor screen to look for specific factor VIII inhibition. If specific inhibition is apparent, it will be titred.

**Useful For:** Detecting the presence of a specific factor inhibitor directed against coagulation factor VIII

**Interpretation:** An interpretive report will be provided when testing is completed.

**Reference Values:**
Only orderable as a reflex. For more information see:
- 8INHE / Factor VIII Inhibitor Evaluation, Plasma
- ALUPP / Lupus Anticoagulant Profile, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- APROL / Prolonged Clot Time Profile, Plasma
- AVWPR / von Willebrand Disease Profile, Plasma

Clinical References:

Coagulation Factor X Activity Assay, Plasma

**Clinical Information:** Factor X is a vitamin K-dependent serine protease that is synthesized in the liver. Its biological half-life is 24 to 48 hours. Factor X participates in both intrinsic and extrinsic pathways of coagulation (final common pathway) by serving as the enzyme (factor Xa) in the prothrombinase complex. Congenital factor X deficiency is rare. Acquired deficiency associated with liver disease, warfarin therapy, vitamin K deficiency, systemic amyloidosis and inhibitors (rare). Deficiency may cause prolonged prothrombin time and activated partial thromboplastin time.

**Useful For:** Diagnosing deficiency of coagulation factor X, congenital or acquired Evaluating hemostatic function in liver disease Investigation of prolonged prothrombin time or activated partial thromboplastin time

**Interpretation:** Acquired deficiency is more common than congenital deficiency. Homozygotes: <25% Heterozygotes: 25% to 50%

**Reference Values:**
Adults: 70-150%
- Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

Clinical References:
2. Brenner B,
Coagulation Factor X Chromogenic Activity Assay, Plasma

Clinical Information: The antithrombotic effect of oral vitamin K antagonists (eg, warfarin) is mediated by reduction in the plasma activity of vitamin K-dependent procoagulant factors II (prothrombin) and X. The intensity of oral anticoagulation therapy with vitamin K antagonists must be monitored and adjusted to a narrow therapeutic range; undermedicating increases the risk of thrombosis, while overmedicating increases the risk of bleeding. Such therapy typically is monitored with the prothrombin time/international normalized ratio (INR) system. Lupus anticoagulants (LAC) are autoantibodies that interfere with phospholipid-dependent clotting tests and most commonly cause prolongation of the activated partial thromboplastin time (APTT). LAC can be associated with a prothrombotic disorder termed the antiphospholipid syndrome. LAC occasionally may cause prolongation of the baseline prothrombin time, rendering the INR system inaccurate for monitoring the intensity of oral anticoagulant therapy. LAC-induced prolongation of the prothrombin time is most commonly seen with recombinant human tissue factor thromboplastins (ie, prothrombin time reagents) with a low international sensitivity index (ISI) such as Innovin or RecombiPlasTin 2G (ISI = 1.0). The chromogenic factor X activity is an alternative assay for monitoring oral anticoagulant therapy. This assay is unaffected by LAC because the assay end point is not a phospholipid-dependent clotting time. Argatroban is a parenteral direct thrombin inhibitor that is approved for treatment of heparin-induced thrombocytopenia (HIT), an antibody-mediated prothrombotic disorder. Argatroban therapy prolongs the prothrombin time, which also renders the INR inaccurate for monitoring the warfarin effect while transitioning from Argatroban to oral anticoagulant therapy. The chromogenic coagulation factor X activity assay may be used as an alternative to the INR for monitoring and adjusting the warfarin dose during this transition.

Useful For: Monitoring warfarin anticoagulant therapy, especially in patients whose plasma contains lupus anticoagulants that interfere with baseline prothrombin time/international normalized ratio and in patients receiving the drug Argatroban who are being transitioned to warfarin This assay should not be used for monitoring heparin, or oral direct factor Xa inhibitors such as rivaroxaban (Xarelto), apixaban (Eliquis), or edoxaban (Savaysa).

Interpretation: A chromogenic factor X activity of approximately 20% to 40% corresponds to the usual warfarin international normalized ratio range (ie, 2.0-3.0).

Reference Values:
> or =18 years of age: 60%-140%

Chromogenic Factor X activity generally correlates with the one-stage factor X activity. In full term or premature neonates, infants, and children, the one-stage factor X activity* is lower than adult reference range and progressively rises to the adult reference range by adolescence. However, no similar data for the chromogenic factor X activity have been published.

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

Coagulation Factor XI Activity Assay, Plasma

**Clinical Information:** Factor XI is synthesized in the liver. Its biological half-life is 60 to 80 hours. Factor XI is a component of intrinsic coagulation pathway which, when activated, activates factor IX to IXa. Factor XI deficiency may cause prolonged partial thromboplastin time. Deficiency associated with mild bleeding diathesis, but there is poor correlation between activity level and clinical bleeding. A relatively high incidence of congenital deficiency occurs among Ashkenazi Jewish descent (hemophilia C).

**Useful For:** Diagnosing deficiency of coagulation factor XI Investigation of prolonged activated partial thromboplastin time

**Interpretation:** Acquired deficiency is associated with liver disease and rarely inhibitors. Patients that are homozygous: <20% activity Patient that are heterozygous: 20% to 60% activity

**Reference Values:**
- Adults: 55-150%
  - Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) which may not reach adult levels for > or =180 days postnatal.*
  - *See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Clinical References:**

Coagulation Factor XII Activity Assay, Plasma

**Clinical Information:** Factor XII is synthesized in the liver. Its biological half-life is 40 to 50 hours. Factor XII is a component of the contact activation system and is involved in both intrinsic pathway and fibrinolytic system. Factor XII deficiency is often discovered when activated partial thromboplastin time is found to be unexpectedly long. The deficiency causes no known bleeding disorder. An association between severe factor XII deficiency and thrombosis risk has been proposed, but not proven.

**Useful For:** Diagnosing deficiency of coagulation factor XII Determining cause of prolonged activated partial thromboplastin time

**Interpretation:** Acquired deficiency is associated with liver disease, nephritic syndrome, and chronic granulocytic leukemia. Congenital homozygous deficiency: 20% activity Congenital heterozygous deficiency: 20% to 50% activity

**Reference Values:**
- Adults: 55-180%
  - Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15% to 20%) which may not reach adult levels for > or =180 days postnatal.*
  - *See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Clinical References:**
**Cobalamin, Methionine, and Methylmalonic Acid Pathways, Plasma**

**Clinical Information:** Homocysteine, methylmalonic acid (MMA), methylocitric acid, methionine, cysteine, and cystathionine can be used to evaluate patients for inborn errors of methionine, cobalamin, and propionate metabolism. Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, developmental delay, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine along with decreased concentrations of cystine. Elevated levels of MMA result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12. Enzymatic deficiencies of propionyl-CoA carboxylase and methylmalonyl-CoA mutase are associated with propionic academia (PA) and methylmalonic acidemia mut(0/-) type (MMAmut), respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMAmut includes elevations of propionyl carnitine, methylmalonic acid, and methylocitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal MMA concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Inherited conditions of cobalamin (Cbl) absorption and transport are caused by variants in several genes encoding Cbl binding factors and transmembrane transporters and receptors. In addition, inside the cell, Cbl undergoes several steps of modification until it reaches a divergent point beyond which 2 separate paths lead to the formation of the 2 active components of this cofactor: a) adenosylcobalamin (AdoCbl), a cofactor for methylmalonyl-CoA mutase; and b) methylcobalamin (MeCbl), a cofactor for methionine synthase (MS), remethylating homocysteine to methionine. Defects of AdoCbl and MeCbl metabolism after the point where the synthetic pathways separate lead to isolated deficiencies of methylmalonyl-CoA mutase (elevations of propionyl carnitine, MMA, and methylocitric acid) or methionine synthase (elevated homocysteine with low/low normal methionine) respectively. Defects prior to this point are associated with deficiencies of both enzymes and lead to elevation of all markers (propionyl carnitine, MMA, MMA, methylocitric acid, and homocysteine).

Acquired cobalamin (vitamin B12) deficiency can be a result of pernicious anemia, vegan diet, malabsorption, and decreased intrinsic factor excretion (secondary to gastrectomy) and can be distinguished from most inherited defects (particularly intracellular deficiencies) with the identification of decreased levels of vitamin B12. Elderly patients with cobalamin deficiency may present with megaloblastic anemia, peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. Additional testing with homocysteine and MMA determinations may help distinguish between vitamin B12 and folate deficiency states.

**Useful For:** Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine, cobalamin, or propionate metabolism using plasma specimens Evaluating individuals with suspected deficiency of vitamin B12

**Interpretation:** An interpretive report will be provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (complementation studies, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, complementation studies) or molecular genetic analyses are required.

**Reference Values:**
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<th>Methyl-malonic acid (nmol/mL)</th>
<th>2-Methylcitric acid (nmol/mL)</th>
<th>Total cysteineMethionine (nmol/mL)</th>
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Current as of June 14, 2021 12:13 pm CDT
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CMMPS 606111

Cobalamin, Methionine, and Methylmalonic Acid Pathways, Serum

Clinical Information: Homocysteine, methylmalonic acid (MMA), methylicitric acid, methionine, cysteine, and cystathionine can be used to evaluate patients for inborn errors of methionine, cobalamin, and propionate metabolism. Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, developmental delay, seizures, thrombembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine along with decreased concentrations of cysteine. Elevated levels of MMA result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12. Enzymatic deficiencies of propionyl-CoA
carboxylase and methylmalonyl-CoA mutase are associated with propionic acidemia (PA) and methylmalonic academia mut(0/-) type (MMAmut), respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMAmut includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal MMA concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Inherited conditions of cobalamin (Cbl) absorption and transport are caused by variants in several genes encoding Cbl binding factors and transmembrane transporters and receptors. In addition, inside the cell, Cbl undergoes several steps of modification until it reaches a divergent point beyond which 2 separate paths lead to the formation of the 2 active components of this cofactor: a) adenosylcobalamin (AdoCbl), a cofactor for methylmalonyl-CoA mutase; and b) methylcobalamin (MeCbl), a cofactor for methionine synthase (MS), remethylating homocysteine to methionine. Defects of AdoCbl and MeCbl metabolism after the point where the synthetic pathways separate lead to isolated deficiencies of methylmalonyl-CoA mutase (elevations of propionyl carnitine, MMA, and methylcitric acid) or methionine synthase (elevated homocysteine, with low/low normal methionine) respectively. Defects prior to this point are associated with deficiencies of both enzymes and lead to elevation of all markers (propionyl carnitine, MMA, methylcitric acid, and homocysteine). Acquired cobalamin (vitamin B12) deficiency can be a result of pernicious anemia, vegan diet, malabsorption, and decreased intrinsic factor excretion (secondary to gastrectomy) and can be distinguished from most inherited defects (particularly intracellular deficiencies) with the identification of decreased levels of vitamin B12. Elderly patients with cobalamin deficiency may present with megaloblastic anemia, peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. Additional testing with homocysteine and MMA determinations may help distinguish between vitamin B12 and folate deficiency states.

**Useful For:** Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine, cobalamin, or propionate metabolism Evaluating individuals with suspected deficiency of vitamin B12

**Interpretation:** An interpretive report will be provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (complementation studies, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, complementation studies) or molecular genetic analyses are required.

**Reference Values:**

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<th>Age</th>
<th>Total homocysteine (nmol/mL)</th>
<th>Methyl-malonic acid (nmol/mL)</th>
<th>2-Methylcitric acid (nmol/mL)</th>
<th>Total cysteine (nmol/mL)</th>
<th>Methionine (nmol/mL)</th>
<th>Cystathionine (nmol/mL)</th>
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<td></td>
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<td>85 years</td>
<td>7.3-16.0 8.2-16.2 0.10-0.48 0.02-0.35 317.9-390.6 20.3-28.7 21.0-27.1 0.11-0.26</td>
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<td>&gt;85 years</td>
<td>7.4-16.0 8.3-16.2 0.10-0.48 0.02-0.35 317.9-390.6 20.3-28.7 21.0-27.1 0.11-0.26</td>
<td>An interpretive report will also be provided.</td>
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**Reference Values:**

0-17 years: not established

> or =18 years: The American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index for cobalt in urine is an end-of-shift concentration of >14.9 mcg/L at the end of the work week.

**Clinical References:**
1. Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists (ACGIH); 2010

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**Cobalt, 24 Hour, Urine**

**Clinical Information:** Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Deupy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting cobalt exposure Monitoring metallic prosthetic implant wear This test is not useful to assess vitamin B12 activity.

**Interpretation:** Concentrations of 2.0 mcg/specimen or more indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/specimen) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is above 5 mcg/specimen, consistent with prosthesis wear. Urine concentrations above 20 mcg/specimen in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**

0-17 years: not established

> or =18 years: 0.2-3.5 mcg/24 hours

**Clinical References:**
3. Lison D, De Boeck M, Verougstraete V,
Cobalt, Blood

Clinical Information: Cobalt (Co) is a naturally occurring, hard, grey element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. One of the radioactive isotopes of cobalt, (60)Co, is used to sterilize medical equipment, in radiation therapy for cancer patients, and to irradiate food. Cobalt is an essential cofactor in vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of cobalt intake. However, more than a million workers are potentially exposed to cobalt and its compounds, with the greatest exposure in mining processes, cemented tungsten-carbide industry, cobalt powder industry, and alloy production industry. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic exposure to cobalt-containing hard metal (dust or fume) can result in a serious lung disease called hard metal lung disease, which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of cobalt particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to cobalt is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. Per FDA recommendations, orthopedic surgeons should consider measuring and following serial cobalt concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. Blood cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring exposure to cobalt using whole blood specimens Monitoring metallic prosthetic implant wear This test is not useful for assessment of vitamin B12 activity.

Interpretation: Concentrations of 1.0 ng/mL and above indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. In the context of failed metal-on-metal prosthetics, elevated cobalt in serum or blood is rarely the initial finding and is often preceded by physical symptoms including reduced range of motion, swelling, inflammation around the joints, and general discomfort or pain. The American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index (BEI) for cobalt in blood is 1 mcg/L (1 ng/mL), which should be collected at the end of shift at the end of the work week.

Reference Values: 0-17 years: not established > or =18 years: <1.0 ng/mL

Cobalt, Serum

Clinical Information: Cobalt is rare but widely distributed in the environment, used in the manufacture of hard alloys with high melting points and resistance to oxidation; cobalt alloys are used in manufacture of some artificial joint prosthesis devices. Cobalt salts are used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is an essential cofactor in vitamin B12 metabolism. Cobalt deficiency has not been reported in humans. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Serum cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt toxicity Monitoring metallic prosthetic implant wear This test is not useful for assessment of vitamin B12 activity.

Interpretation: Concentrations greater than or equal to 1.0 ng/mL indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. If cobalt is ingested, concentrations greater than 5 ng/mL suggest major exposure and likely toxicity. If cobalt exposure is due to orthopedic implant wear, there are no large case number reports associating high circulating serum cobalt with toxicity. There are no Occupational Health and Safety Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (4-10 ng/mL) in serum cobalt concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with cobalt-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. However, the FDA recommends testing cobalt in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal implants.

Reference Values:
<1.0 ng/mL
<10.0 ng/mL (Metal-on-metal implant)

Reference values apply to all ages.

The reported unit of measurement for cobalt of ng/mL is equivalent to mcg/L.

Cobalt, Synovial Fluid

**Clinical Information:** Per FDA recommendations, orthopedic surgeons should consider measuring and following serial Co concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. However, a recent publication(1) has shown synovial fluid measurements were superior to whole blood and serum Co concentrations in predicting local tissue destruction in failed hip arthroplasty constructs. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, Co, and molybdenum. This list of products is incomplete, and these products' compositions change occasionally; see each prostheses' product information for composition details. Cobalt (Co) is a naturally occurring, hard, grey element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Co is an essential cofactor for vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of Co intake. The greatest environmental exposure occurs in mining processes, cemented tungsten-carbide industry, Co powder industry, and alloy production industry. Co is not highly toxic; however large doses may produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic exposure to Co-containing hard metal (dust or fume) can result in a serious lung disease called “hard metal lung disease,” which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of Co particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to Co is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. In cases of suspected toxicity, blood, serum, or urine concentrations of Co can be checked. Vitamin B12 should be used to assess nutritional status.

**Useful For:** Monitoring metallic prosthetic implant wear and local tissue destruction in failed hip arthroplasty constructs This test is not useful for assessment of nutritional status or potential cobalt toxicity.

**Interpretation:** Based on an internal study, synovial fluid cobalt concentrations of 17.2 ng/mL or above were more likely due to a metal reaction (eg, adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 80.8% and specificity of 81.5%).

**Reference Values:**
- 0-17 years: Not established
- > or =18 years: <17.2 ng/mL

**Clinical References:**

Cobalt/Creatinine Ratio, Random, Urine

**Clinical Information:** Cobalt (Co) is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were
sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Deupuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting cobalt exposure in a random urine collection Monitoring metallic prosthetic implant wear This test is not useful for assessment of vitamin B12 activity.

**Interpretation:** Concentrations greater or equal to 2.0 mcg/g creatinine indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/g creatinine) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is greater than 5 mcg/g creatinine, consistent with prosthesis wear. Urine concentrations greater than 20 mcg/g creatinine in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**

- 0-17 years: Not established
- >17 years: <1.7 mcg/g Creatinine

**Clinical References:**


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**FCOKE 75174**

**Cocaine Analysis - Whole Blood**

**Reference Values:**

- **Cocaine Screen:**
  - Cocaine and Metabolite, UA â£±,â£¢ Negative; Cutoff: 25 ng/mL

- **Cocaine Confirmation:**
  - Cocaine
  - Benzoylecgonine
  - Confirmation threshold: 10 ng/mL

**COKMX 62720**

**Cocaine and Metabolite Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and to a lesser extent in India, Africa, and Java. (1) Cocaine is a
powerfully addictive stimulant drug. Cocaine abuse has a long history and is rooted into the drug culture in the United States,(2) and is one of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly ethanol, and the simultaneous use of both drugs can be determined by the presence of the unique metabolite cocaethylene.(4) Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(7) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(8) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(7) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

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

**Interpretation:** The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at \( > \ or = 50 \text{ ng/g} \) is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

- **Negative**
  - Positives are reported with a quantitative LC-MS/MS result.
  - Cutoff concentrations
  - Cocaine by LC-MS/MS: 50 ng/g
  - Benzoylecgonine by LC-MS/MS: 50 ng/g
  - Cocaethylene by LC-MS/MS: 50 ng/g
  - m-Hydroxybenzoylecgonine by LC-MS/MS: 50 ng/g

**Clinical Information:** Cocaine is a drug of current health concern because of its proliferation among recreational drug abusers. Freebase and crack increase the potential for major cocaine toxicity. Cocaine use is declining across the nation according to the National Institute of Drug Abuse. Increasingly, laboratory results are disputed or there are medical/legal overtones. Therefore, physicians are finding an increased need to confirm positive results before informing or confronting the patients. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detecting and confirming drug abuse involving cocaine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Reports will specifically indicate the presence or absence of cocaine and benzoylecgonine. The presence of cocaine, or its major metabolite, benzoylecgonine, indicates use within the past 4 days. Cocaine has a 6-hour half-life, so it will be present in urine for 1 day after last use. Benzoylecgonine has a half-life of 12 hours, so it will be detected in urine up to 72 hours after last use. There is no correlation between concentration and pharmacologic or toxic effects.

**Reference Values:**

- **Negative**
- Positives are reported with a quantitative GC-MS result.
- Cutoff concentrations:

  - **IMMUNOASSAY SCREEN**
    - $<150$ ng/mL
  - **COCAINE BY GC-MS**
    - $<50$ ng/mL
  - **BENZOYLECGONINE BY GC-MS**
    - $<50$ ng/mL

**Clinical References:**
Positive results are reported with a quantitative GC-MS result.

Cutoff concentrations:

COCAINE BY GC-MS
<50 ng/mL

BENZOYLECGONINE BY GC-MS
<50 ng/mL

**Clinical References:**

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**COKEM**

**Cocaine and Metabolites Confirmation, Meconium**

**Clinical Information:** Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and to a lesser extent in India, Africa, and Java.(1) Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history and is rooted into the drug culture in the United States,(2) and is 1 of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly ethanol, and the simultaneous use of both drugs can be determined by the presence of the unique metabolite cocaethylene.(4) Intraterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(7) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(8) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(7)

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

**Interpretation:** The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at 50 ng/g or more is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

Negative

Positives are reported with a quantitative LC-MS/MS result.

Cutoff concentrations

Cocaine by LC-MS/MS: 50 ng/g
Benzoylecgonine by LC-MS/MS: 50 ng/g
Cocaethylene by LC-MS/MS: 50 ng/g
m-Hydroxybenzoylecgonine by LC-MS/MS: 50 ng/g

**Clinical References:**
RSCOC

Coccidioides Antibody Reflex, Complement Fixation and Immunodiffusion, Serum

Clinical Information: Coccidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern US, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis/posadasii. Usually, it is a mild, self-limiting pulmonary infection. Less commonly, chronic pneumonia may occur, progressing to fibronodular, cavitory disease. A rash often develops within a day or 2, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs, including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgM precipitating antibodies. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningial infection and have lived or traveled in areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: Detection of antibodies to Coccidioides species

Interpretation: Complement Fixation: Titers of 1:2 or higher may suggest active disease; however, titers may persist for months after infection has resolved. Increasing complement fixation (CF) titers in serial specimens are considered diagnostic of active disease. Immunodiffusion: The presence of IgM antibody may be detectable within 2 weeks after the onset of symptoms; however, antibody may be detected longer than 6 months after infection. The presence of IgG antibody parallels the CF antibody and may suggest an active or a recent asymptomatic infection with Coccidioides immitis/posadasii; however, antibodies may persist after the infection has resolved. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. Over 90% of primary symptomatic cases will be detected by combined immunodiffusion (ID) and CF testing.

Reference Values:
Only orderable as a reflex. For more information see COXIS / Coccidioides Antibody Screen with Reflex, Serum.

COMPLEMENT FIXATION:
Negative
If positive, results are titered.

IMMUNODIFFUSION:
Negative
Results are reported as positive, negative, or equivocal.

**Clinical Information:** Coccidioidomycosis (valley fever, San Joaquin Valley fever, desert rheumatism) is caused by the dimorphic fungus Coccidioides immitis/posadasii, which is found in the southwestern US, regions in the northwestern US, and in Central and South America. It is acquired by inhalation of airborne Coccidioides arthroconidia. The majority of infections are subclinical. Among symptomatic patients, the majority will present acute flulike, pulmonary symptoms approximately 7 to 28 days post exposure. Symptoms may include chest pain, cough, fever, malaise, and lymphadenopathy.(1) A rash often develops within a couple of days, followed by erythema nodosum or multiforme with accompanying arthralgia. A pulmonary lesion or nodule may develop months following infection and may be a source of infection if the patient becomes immunosuppressed in the future. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. Individuals at greater risk for dissemination include African Americans, patients of Filipino descent, pregnant women, and immunocompromised patients.(2) Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

**Useful For:** Detection of antibodies to Coccidioides immitis/posadasii This assay should not be used as a screen for the general population nor for monitoring response to therapy.

**Interpretation:** Enzyme immunoassay (EIA) results greater than or equal to 0.75 will be reported as Reactive: Confirmatory testing by complement fixation and immunodiffusion has been ordered. A reactive result is presumptive evidence that the patient was previously or is currently infected with Coccidioides immitis/posadasii. EIA results less than 0.75 will be reported as Negative: A single negative result does not exclude the diagnosis of coccidioidomycosis. Repeat testing on a new sample in 7 to 14 days if clinically indicated. A negative result indicates the absence of antibodies to Coccidioides immitis/posadasii and is presumptive evidence that the patient has not been previously exposed to and is not infected with Coccidioides. However, a negative result does not preclude the diagnosis of coccidioidomycosis as the specimen may have been drawn before antibodies levels were detectable due to early acute infection or immunosuppression. This test is designed for the qualitative detection of both IgM- and IgG-class antibodies against antigens from Coccidioides. The report will not indicate which class of antibody is present.

**Reference Values:**

Negative

Reference value applies to all ages


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**SCOC 8295**

**Coccidioides Antibody, Complement Fixation and Immunodiffusion, Serum**

**Clinical Information:** Coccidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern US, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis/posadasii. Usually, it is a mild, self-limiting pulmonary infection. Less commonly, chronic pneumonia may occur, progressing to fibronodular, cavitory disease. A rash often develops within a day or 2, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs, including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgG precipitating antibodies. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where C immitis/posadasii is endemic. Any history of...
exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: Diagnosis of coccidioidomycosis in serum specimens

Interpretation: Complement Fixation: Titers of 1:2 or higher may suggest active disease; however, titers may persist for months after infection has resolved. Increasing complement fixation (CF) titers in serial specimens are considered diagnostic of active disease. Immunodiffusion: The presence of IgM antibody may be detectable within 2 weeks after the onset of symptoms; however, antibody may be detected longer than 6 months after infection. The presence of IgG antibody parallels the CF antibody and may suggest an active or a recent asymptomatic infection with Coccidioides immitis/posadasii; however, antibodies may persist after the infection has resolved. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. Over 90% of primary symptomatic cases will be detected by combined immunodiffusion (ID) and CF testing.

Reference Values:

COMPLEMENT FIXATION
- Negative
- If positive, results are titered.

IMMUNODIFFUSION
- Negative
- Results are reported as positive, negative, or equivocal.


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Coccidioides Antibody, Complement Fixation and Immunodiffusion, Spinal Fluid

Clinical Information: Coccidioidomycosis (Valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern United States, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis/posadasii. Usually, it is a mild, self-limiting pulmonary infection. Less commonly, chronic pneumonia may occur, progressing to fibronodular cavitary disease. A rash often develops within 1 to 2 days, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs, including the meninges. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of meningal infection and have lived in or traveled to areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when coccidioidomycosis serologic tests are being considered.

Useful For: Diagnosing coccidioidomycosis in spinal fluid

Interpretation: Complement Fixation: IgG antibody is detected by complement fixation (CF) testing. Any CF titer in cerebrospinal fluid (CSF) should be considered significant. A positive complement fixation test in un-concentrated CSF is diagnostic of meningitis. Immunodiffusion: IgM and IgG precipitins are rarely found in CSF. However, when present, they are diagnostic of meningitis (100% specific). Since the immunodiffusion test is 100% specific, it is helpful in interpreting CF results.

Reference Values:

COMPLEMENT FIXATION
- Negative
If positive, results are titered.

IMMUNODIFFUSION
Negative
Results are reported as positive, negative, or equivocal.


Coccidioides immitis/posadasii, Molecular Detection, PCR, Paraffin, Tissue

Clinical Information: Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America. The illness commonly manifests as a self-limited upper respiratory tract infection, but can also result in disseminated disease that may be refractory to treatment.(1) Clinical onset generally occurs 10 to 16 days following inhalation of coccidioidal spores (arthroconidia).(2) Disease progression may be rapid in previously healthy or immunosuppressed individuals. At present, the gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens. Culture is highly sensitive and, with the implementation of DNA probe assays for confirmatory testing of culture isolates, yields excellent specificity.(3) However, growth in culture may take up to several weeks. This often delays the diagnosis and treatment of infected individuals. Serological tests including immunodiffusion and complement fixation are widely used for the detection of antibody against Coccidioides. Serology for Coccidioides can be limited by delays in antibody development or nonspecificity due to cross-reactions with other fungi. In addition, immunodiffusion and complement fixation tests are highly labor intensive and are generally limited to reference laboratories. Molecular methods can identify Coccidioides species directly from clinical specimens and should be used in conjunction with culture. For specimen types such as formalin-fixed, paraffin-embedded tissue, culture is not possible, but the molecular test may provide useful information.

Useful For: Rapid detection of Coccidioides DNA Aiding in the diagnosis of coccidioidomycosis

Interpretation: A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA. An inhibition result indicates that the detection of Coccidioides DNA is inhibited in this specimen. A new specimen can be resubmitted under a new order, if desired.

Reference Values: Not applicable


Coccidioides immitis/posadasii, Molecular Detection, PCR, Varies

Clinical Information: Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America. The illness commonly manifests as a self-limited upper respiratory tract infection, but can also result in disseminated disease that may be refractory to treatment.(1) Clinical onset generally occurs 10 to 16 days following inhalation of coccidioidal spores (arthroconidia).(2) Disease progression may be rapid in previously healthy or immunosuppressed individuals. At present, the gold standard for the diagnosis of coccidioidomycosis is
culture of the organism from clinical specimens. Culture is highly sensitive and, with the implementation of DNA probe assays for confirmatory testing of culture isolates, yields excellent specificity. However, growth in culture may take up to several weeks. This often delays the diagnosis and treatment of infected individuals. In addition, the propagation of Coccidioides species in the clinical laboratory is a significant safety hazard to laboratory personnel, serving as an important cause of laboratory-acquired infections if the organism is not quickly identified and handled appropriately (i.e., in a Biosafety Level 3 facility). Serological tests including immunodiffusion and complement fixation are widely used for the detection of antibody against Coccidioides. Serology for Coccidioides can be limited by delays in antibody development or nonspecificity due to cross-reactions with other fungi. In addition, immunodiffusion and complement fixation tests are highly labor intensive and are generally limited to reference laboratories. Molecular methods can identify Coccidioides species directly from clinical specimens, allowing for a more rapid diagnosis. Fungal culture should also be performed since the isolate may be needed for antifungal susceptibility testing.

**Useful For:** Rapid detection of Coccidioides DNA, preferred method

**An aid in diagnosing coccidioidomycosis**

**Interpretation:** A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA.

**Reference Values:**
Not applicable


**FCKTF**

**Cockatiel Feathers IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**CBUR**

**Cocklebur, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing a diagnosis of an allergy to cocklebur Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.10</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Cockroach American (Periplaneta americana) IgE**

**Clinical Information:** This assay is used to detect allergen specific-IgE using the ImmunoCAP® FEIA method. In vitro allergy testing is the primary testing mode for allergy diagnosis.

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

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**Cockroach, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to cockroach Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

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

Reference Values:

Class IgE kU/L     Interpretation
0                 Negative
1 0.35-0.69        Equivocal
2 0.70-3.49        Positive
3 3.50-17.4        Positive
4 17.5-49.9        Strongly positive
5 50.0-99.9        Strongly positive
6 > or =100        Strongly positive Reference values apply to all ages.


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Coconut IgG

Interpretation:

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

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Coconut, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to coconut Defining the allergen responsible for
eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<tr>
<td>4</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Codfish, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to codfish Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

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

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Coenzyme Q10, Reduced and Total, Plasma

Clinical Information: Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation where it functions as an electron carrier and acts as an antioxidant. It is found in all cell membranes and is carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein (HDL), and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent on both its concentration and its reduction-oxidation (redox) status. CoQ10 deficiencies, which are clinically and genetically diverse, can occur due to defects in genes involved in the biosynthesis of ubiquinone (primary CoQ10 deficiency) or due to other causes such as mitochondrial disorders (secondary or CoQ10 deficiency). Five major clinical phenotypes of CoQ10 deficiency have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Severe multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Glomerulopathy -Isolated myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies can improve mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including Parkinson disease, diabetes, and Alzheimer disease, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy; changes in CoQ10 may be relevant to statin-induced myalgia. Additionally, the redox status of CoQ10 may be a useful early marker for the detection of oxidative LDL modification.

Useful For: Diagnosis of primary CoQ10 deficiencies in some patients who are not supplemented with CoQ10 Diagnosis of coenzyme Q10 (CoQ10) deficiency in mitochondrial disorders Monitoring CoQ10 status during treatment of various degenerative conditions including Parkinson and Alzheimer disease This test is not useful for distinguishing primary CoQ10 deficiencies from acquired CoQ10 deficiencies.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
CoQ10 REDUCED
<18 years: 320-1,376 mcg/L
> or =18 years: 415-1,480 mcg/L

CoQ10 TOTAL
<18 years: 320-1,558 mcg/L
> or =18 years: 433-1,532 mcg/L

CoQ10 % REDUCED
<18 years: 93-100%
> or =18 years: 92-98%


TQ10 63148

Coenzyme Q10, Total, Plasma

Clinical Information: Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation, where it functions as an electron carrier and also acts as an antioxidant. It is found in all cell membranes and carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein (HDL), and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent on both its concentration and reduction-oxidation (redox) status. CoQ10 deficiencies, which are clinically and genetically diverse, can occur due to defects in genes involved in the biosynthesis of ubiquinone (primary CoQ10 deficiency) or due to other causes such as mitochondrial disorders (secondary CoQ10 deficiency). Five major clinical phenotypes of CoQ10 deficiency have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Severe multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Glomerulopathy -Isolated myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies can improve mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including Parkinson disease, diabetes, and Alzheimer disease, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy; changes in CoQ10 may be relevant to statin-induced myalgia. Additionally, the redox status of CoQ10 may be a useful early marker for the detection of oxidative LDL modification.

Useful For: Diagnosis of primary CoQ10 deficiencies in some patients who are not supplemented with CoQ10 Monitoring patients receiving statin therapy Monitoring CoQ10 status during treatment of various degenerative conditions including Parkinson and Alzheimer disease Hemolyzed specimens to provide accurate quantitation of total coenzyme Q10 This test is not useful for distinguishing primary CoQ10 deficiencies from acquired CoQ10 deficiencies

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
TOTAL CoQ10
<18 years: 320-1,558 mcg/L
> or =18 years: 433-1,532 mcg/L

Miles MV, Horn PS, Tang PH, et al: Age-related changes in plasma coenzyme Q10 concentrations and


FCOF 57525

Coffee (Coffea spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.1 0.34 Equivocal 1 0.35 0.69 Low Positive 2 0.70 1.74 Moderate Positive 3 3.5 4.9 Very High Positive 4 4.9 17.4 Very High Positive 5 17.5 49.9 Very High Positive 6 49.9 175 Very High Positive

Reference Values:
<0.35 kU/L

ML20C 605263

COG Metaphases, 1-19 (Bill Only)

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

M25C 605264

COG Metaphases, 20-25 (Bill Only)

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

MG25C 605265

COG Metaphases, >25 (Bill Only)

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

CATR 113385

Cold Agglutinin Titer, Serum

Clinical Information: The cold agglutinin titer test is to be used as a tool in the evaluation of suspected cold agglutinin syndrome. In this syndrome, cold agglutinins, usually IgM with anti-I specificity, attach to the patient's erythrocytes causing a variety of symptoms. Symptoms may include chronic anemia due to premature removal of the sensitized erythrocytes from circulation by hemolysis, to acrocyanosis of the ears, fingers, or toes due to local blood stasis in the skin capillaries.

Useful For: Detection of cold agglutinins in patients with suspected cold agglutinin disease

Interpretation: Patients with cold agglutinin syndrome usually exhibit a titer value greater than
1:512, with rare cases reportedly as low as 1:64. Normal individuals often have low levels of cold agglutinins. The test is not a direct measure of clinical significance and must be used in conjunction with other in vitro and in vivo parameters.

**Reference Values:**

<1:64

**Clinical References:**


**Collagen IV Immunostain, Technical Component Only**

**Clinical Information:** Collagen IV stains the basal lamina of capillaries as well as basement membrane structures in all organs. In the kidney, the antibody stains the glomerular and tubular basement membranes and mesangial cells and matrix within the glomerulus.

**Useful For:** A marker of the basal lamina of capillaries and basement membranes in all organs

**Interpretation:** This test does not includes pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


**Collagen Type II Antibodies**

**Interpretation:** Anti-collagen II antibodies occur in 22% of patients with idiopathic SNHL, 30% of patients with sudden deafness and 20% of patients with Meniere’s disease. Anti-collagen II antibodies also occur in patients with relapsing polychondritis and in rheumatoid arthritis.

**Reference Values:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Negative</td>
<td>&lt;20 EU/mL</td>
</tr>
<tr>
<td>Borderline/Equivocal</td>
<td>20-25 EU/mL</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;25 EU/mL</td>
</tr>
</tbody>
</table>

**Collapsin Response-Mediator Protein-5-IgG, Western Blot, Serum**

**Clinical Information:** Autoantibodies specific for neurons and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic when diagnosed, but usually limited in spread to regional lymph nodes and adjacent structures. (1-4) Collapsin response-mediator protein-5 (CRMP-5) is highly expressed in small-cell lung carcinomas (SCLC), in neurons throughout the adult central and peripheral nervous systems, and in a subset of glial cells. (1) In Western blot analyses the native antigen is a 62-kDa protein (recombinant human CRMP-5 is 68-kDa). (1) CRMP-5-IgG (also known as anti-CV-2)(4,5) is a more common
autoantibody accompaniment of SCLC than antineuronal nuclear antibodies-1 (ANNA-1; anti-Hu) and sometimes occurs with thymoma. The neurological presentation of CRMP-5 seropositive patients is usually multifocal, and can affect any level of the neuraxis. Neurological presentations that suggest a CRMP-5-IgG-related syndrome include subacute chorea or cranial neuropathy (particularly loss of vision, taste, or smell), dementia, myelopathy and gastrointestinal dysmotility in a patient with risk factors for lung cancer, or encephalopathy or neuromuscular hyperexcitability in a patient with serological or clinical evidence of myasthenia gravis.(1) Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma usually present with other myasthenia gravis neurological manifestations (eg, encephalopathy, disorders of continuous muscle fiber activity).(3) CRMP-5-IgG is defined in serum or spinal fluid (CSF) by its characteristic immunofluorescence (IF) staining pattern on a mixed tissue substrate of adult mouse central and peripheral neurons. However, CRMP-5-IgG is not detectable by standard IF screening if the titer is low (serum <1:240; CSF <1:2) or if coexisting autoantibodies, either neuron-specific or nonorgan-specific antinuclear and antimitochondrial antibodies, preclude identification of CRMP-5-IgG with certainty. In these situations, CRMP-5-IgG may be detected by Western blot analysis.

**Useful For:** Evaluation of cases of chorea, vision loss, cranial neuropathy and myelopathy

**Interpretation:** A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis, and is likely to be associated with a small-cell lung carcinoma (SCLC) or thymoma, which may be occult.(1,2) A positive result has a predictive value of 90% for neoplasm (77% SCLC, 6% thymoma).(1) Seropositivity is found in approximately 3% of patients who have SCLC with limited metastasis without evidence of neurological autoimmunity.(6) Clinical-serological correlations have not yet been established for children. Western blot analysis is indicated when interfering nonorgan-specific or coexisting neuron-specific autoantibodies in serum or spinal fluid preclude unambiguous detection of CRMP-5-IgG by indirect immunofluorescence assay, or when the immunofluorescence assay is negative in a patient whose neurological presentation suggests a CRMP-5-IgG-related syndrome.

**Reference Values:**

Negative

**Clinical References:**

factors for lung cancer, or encephalopathy or neuromuscular hyperexcitability in a patient with serological or clinical evidence of myasthenia gravis.(1) Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma usually present with other myasthenia gravis neurological manifestations (eg, encephalopathy, disorders of continuous muscle fiber activity).(3) CRMP-5-IgG is defined in serum or spinal fluid (CSF) by its characteristic immunofluorescence (IF) staining pattern on a mixed tissue substrate of adult mouse central and peripheral neurons. However, CRMP-5-IgG is not detectable by standard IF screening if the titer is low (serum <1:240; CSF <1:2) or if coexisting autoantibodies, either neuron-specific or nonorgan-specific antinuclear and antimitochondrial antibodies, preclude identification of CRMP-5-IgG with certainty. In these situations, CRMP-5-IgG may be detected by Western blot analysis.

**Useful For:** Evaluation of cases of chorea, vision loss, cranial neuropathy and myelopathy

**Interpretation:** A positive result confirms that a patient’s subacute neurological disorder has an autoimmune basis and is likely to be associated with a small-cell lung carcinoma (SCLC) or thymoma, which may be occult.(1,2) A positive result has a predictive value of 90% for neoplasm (77% SCLC, 6% thymoma).(1) Seropositivity is found in approximately 3% of patients who have SCLC with limited metastasis without evidence of neurological autoimmunity.(6) Clinical-serological correlations have not yet been established for children.

**Reference Values:**

Negative

**Clinical References:**


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**MITOT 65212 Combined Mitochondrial Analysis, Mitochondrial Full Genome and Nuclear Gene Panel, Varies**

**Clinical Information:** The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to variants in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to analyze 176 nuclear-encoded genes implicated in mitochondrial disease and to determine the exact sequence of the entire 16,569 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of mitochondrial diseases that result from variants in both nuclear encoded genes and in the mitochondrial genome. Those diseases involving nuclear genes include disorders of mitochondrial protein synthesis, coenzyme Q10 biosynthesis, respiratory chain complexes, and mtDNA maintenance (ie, mitochondrial DNA depletion disorders). Disorders of the mitochondrial genome include those caused by point alterations, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial myopathy (MM), neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP), Leigh syndrome, Leber hereditary optic neuropathy (LHON), and chronic progressive external ophthalmoplegia (CPEO). In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayre or Pearson syndromes, are also detected. In contrast to variants in nuclear genes, which are present in either 0, 1, or 2 copies,
mitochondrial variants can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of altered mitochondria present with more severe disease than those with lower percentages of altered alleles. The sensitivity for the detection of altered alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%. See Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel in Special Instructions for details regarding the targeted nuclear genes identified by this test.

**Useful For:** Diagnosis of mitochondrial disease that results from variants in either nuclear-encoded genes or the mitochondrial genome. A second-tier test for patients in whom previous targeted gene variant analyses for specific mitochondrial disease-related genes were negative. Identification of variants known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. For mitochondrial DNA (mtDNA) alterations, the degree of heteroplasmy of each single nucleotide or INDEL (insertion/deletion) variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Large mtDNA deletions will be reported as either homoplasmic or heteroplasmic, but the degree of heteroplasmy will not be estimated, due to possible preferential amplification of the smaller deletion product by long-range PCR.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CMIL 82833**

**Common Millet, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to common millet. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**Common Reed, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to common reed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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Current as of June 14, 2021 12:13 pm CDT     800-533-1710 or 507-266-5700 or mayocliniclabs.com
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


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**Common Variable Immunodeficiency Confirmation Flow Panel, Blood**

**Clinical Information:** Common variable immunodeficiency (CVID) is the most prevalent primary immunodeficiency with a prevalence of CVID of 1:25,000 to 1:50,000.(1) It has a bimodal presentation with a subset presenting in early childhood and a second set presenting between 15 and 40 years of age or even later. CVID is characterized by hypogammaglobulinemia usually involving most or all of the immunoglobulin (Ig) classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1) B cell numbers are usually normal, although a minority of patients (5%-10%) have very low B cell counts (<1% of peripheral blood leukocytes). It is reasonable to suspect a transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) defect in patients with low to absent IgA, low IgG, and low or normal IgM, along with splenomegaly, autoimmune cytopenias, autoimmune thyroiditis, and tonsillar hypertrophy. In TACI-deficient patients, there may be an increased risk for developing neoplasias such as non-Hodgkin lymphoma or other solid tumors. CD19 defects result in absence of B cells expressing CD19. When an alternative B-cell marker such as CD20 is used, however, B cells can be detected in the blood of these patients. Inducible T-cell costimulator (ICOS)-deficiency results in reduced class-switched memory B-cells. Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4/CD8 ratio (<1).(1) A subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T cell deficiency.(1) Patients with mutations in the TACI gene (see below) are particularly prone to developing autoimmune disease, including cytopenias as well as lymphoproliferative disease. The etiology of CVID is heterogeneous, but recently 4 genetic defects were described that are associated with the CVID phenotype. Specific mutations, all of which are expressed on B cells, have been implicated in the pathogenesis of CVID. These mutations encode for: -ICOS: inducible costimulator expressed on activated T cells(2) -TACI: transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor(3) -CD19(4) -BAFF-R: B-cell activating factor belonging to the tumor necrosis factor (TNF) receptor family(5) Of these, mutations of the gene that encodes TACI, TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B), probably account for about 10% to 15% of all CVID cases.(3) Patients with mutations in the TACI gene are particularly prone to developing autoimmune disease, including cytopenias, as well as lymphoproliferative disease. The other mutations each have been reported in only a handful of patients. The etiopathogenesis is still undefined in more than 75% to 80% of CVID patients. A BAFF-R defect should be suspected in patients with low to very low class switched and nonswitched memory B cells and very high numbers of transitional B cells (see IABC / B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood). Class switching is the process that allows B cells, which possess IgD and IgM on their cell surface as a part of the antigen-binding complex, to produce IgA, IgE, or IgG antibodies. A TACI defect is suspected in patients with low IgA and low IgG with normal to low switched B cells, with autoimmune or lymphoproliferative manifestations or both, and normal B cell responses to mitogens.

**Useful For:** Screening for common variable immunodeficiency (CVID) Identifying defects in TACI and BAFF-R in patients presenting with clinical symptoms and other laboratory features consistent with CVID Evaluating B cell immune competence by assessing expression of BAFF-R and TACI proteins Useful for assessing BAFF-R and TACI protein expression and frequency of B cells bearing these...
receptors. TNFRSF13C (BAFF-R) and TNFRSF13B (TACI) gene mutations have been described in a small subset of patients with humoral immunodeficiencies classified as CVID. The majority of TNFRSF13B mutations preserve TACI protein expression and require genetic testing to identify pathogenic or potentially pathogenic mutations/variants.

**Interpretation:** BAFF-R is normally expressed on over 95% of B cells, while TACI is expressed on a smaller subset of B cells (3%-70%) and some activated T cells. Expression on B cells increases with B cell activation. The lack of TACI or BAFF-R surface expression on B cells is suggestive of a potential common variable immunodeficiency (CVID)-associated defect, if other features of CVID are present. The majority of TACI mutations (>95%) preserve protein expression but abrogate protein function, hence the only way to conclusively establish a TACI mutational defect is to perform genetic testing (TACIF / Transmembrane Activator and CAML Interactor [TACI] Gene, Full Gene Analysis).

**Reference Values:**

| CD19+TACI+ | >3.4% |
| CD19+BAFF-R+ | >90.2% |

Reference values apply to all ages.

**Clinical References:**

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**Complement 4d (C4d, Comp 4d) Immunostain, Technical Component Only**

**Clinical Information:** Complement 4d (C4d) is a split product resulting from complement activation. The deposition of C4d on the walls of peritubular capillaries in kidney allografts or capillaries in cardiac allografts has been associated with antibody-mediated transplant rejection.

**Useful For:** Aids in the identification of antibody-mediated transplant rejection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Complement C1q, Serum**

**Clinical Information:** The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1, C2, C4) results in an inability to clear immune complexes. Inherited deficiency of C1 is rare. Like the more common C2 deficiency, C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus, polymyositis, glomerulonephritis, and Henoch-Schonlein purpura). Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton and common variable hypogammaglobulinemia and severe combined immunodeficiency). This is most likely due to increased catabolism. The measurement of C1q is an indicator of the amount of C1 present.

**Useful For:** Assessment of an undetectable total complement (CH50) level Diagnosing congenital C1 (first component of complement) deficiency Diagnosing acquired deficiency of C1 inhibitor

**Interpretation:** An undetectable C1q in the presence of an absent total complement (CH50) and normal C2, C3, and C4 suggests a congenital C1 (first component of complement) deficiency. A low C1q in combination with a low C1 inhibitor and low C4 suggests an acquired C1 inhibitor deficiency.

**Reference Values:**
12-22 mg/dL

**Clinical References:**

**Complement C3, Serum**

**Clinical Information:** The complement system is an integral part of the body's immune defenses. The primary complement pathway consists of recognition (C1q, C1r, C1s), activation (C4, C2, C3), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. The complement system can be activated via immune complexes, and the alternative pathway (properdin pathway), which is activated primarily by foreign bodies such as microorganisms. C3 activation involves cleavage by C3 convertase into C3a and C3b. When immune complexes are not involved, the alternate method of complement activation initiates the reactant sequence at C3, bypassing C1, C4, and C2. Severe recurrent bacterial infections occur in patients with homozygous C3 deficiency and in those patients with low levels of C3 secondary to the absence of C3b activator. Decreased C3 may be associated with acute glomerulonephritis, membranoproliferative glomerulonephritis, immune complex disease, active systemic lupus erythematosus, septic shock, and end-stage liver disease.

**Useful For:** Assessing disease activity in systemic lupus erythematosus (SLE) Investigating an undetectable total complement (CH50) level

**Interpretation:** A decrease in C3 levels to the abnormal range is consistent with disease activation in systemic lupus erythematosus (SLE).

**Reference Values:**
75-175 mg/dL

**Clinical References:**
**Clinical Information:** The complement system is an integral part of the immune defenses. It can be activated via immune complexes (classic pathway) or by bacterial polysaccharides (alternative pathway). The classic complement pathway consists of recognition, (C1q, C1r, C1s), activation (C2, C3, C4), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. C4 is one of the activation proteins of the classic pathway. In the absence of C4, immune complexes will not be cleared by C3 activation peptides, but bacterial infections can still be defended via the alternative pathway. C4 may be decreased in systemic lupus erythematosus, early glomerulonephritis, immune complex disease, cryoglobulinemia, hereditary angioedema, and congenital C4 deficiency.

**Useful For:** Investigating an undetectable total complement (CH50) Confirming hereditary angioedema (with low C1 inhibitor) Assessing disease activity in systemic lupus erythematosus, proliferative glomerulonephritis, rheumatoid arthritis, and autoimmune hemolytic anemia

**Interpretation:** C4 levels will be decreased in acquired autoimmune disorders, in active phase of lupus erythematosus, and in rheumatoid arthritis. An undetectable C4 level (with normal C3) suggests a congenital C4 deficiency. Levels will be increased in patients with autoimmune hemolytic anemia.

**Reference Values:**
14-40 mg/dL

**Clinical References:**
Complement-Mediated Atypical Hemolytic-Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) Gene Panel, Variies

Clinical Information: Complement-mediated hemolytic uremic syndrome, also known as atypical hemolytic uremic syndrome (aHUS), is a well-recognized disease entity characterized by complement activation in the microvasculature. Abnormalities of the alternate pathway of complement, which may be inherited (genetic) or acquired, underlie both the sporadic and familial forms of the disease and are identified in at least two-thirds (approximately 60%) of patients. Unlike many other monogenic disorders of the immune system, multiple hits may be required for disease manifestation, which may include a trigger event (transplantation, pregnancy, malignant hypertension, autoimmune disorders, sepsis, malignancy, etc), and 1 or more contributing genetic variants or haplotypes in the alternate pathway complement genes. The overall prognosis is poor with most patients developing end-stage renal disease (ESRD) or permanent kidney injury within 1 year of diagnosis despite plasma exchange (PLEX/PEX) or plasma infusion (PI) therapy. Renal transplantation in most patients is also associated with a poor prognosis with loss of the allograft. Drugs targeting the complement pathway, notably Eculizumab, have achieved success in modulating clinical remission and there are a few reports of combined liver-kidney transplants for these patients. Newer therapies are also likely to emerge over time. Individuals with genetic aHUS frequently experience relapse even after complete recovery following the presenting episode. Complement-mediated HUS presents with clinical features that are nearly identical to thrombotic thrombocytopenic purpura (TTP) and Shiga-toxin HUS (ST-HUS), making laboratory differentiation essential. TTP is a rare clinical entity but is an important diagnosis as it is associated with very high mortality (90%) if untreated. Mortality can be reduced by early PLEX. Congenital TTP is due to genetic defects in the ADAMTS13 gene, while acquired TTP is related to autoantibodies against ADAMTS13, which reduces function. While TTP was initially characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurological signs, renal failure and fever, the disease can present with only some of these features. The thrombotic microangiopathies (TMA) cover both aHUS and TTP and the clinical distinctions are not always clear-cut. Besides the thrombocytopenia, which is one of the key features of TMA, there is presence of schistocytes and highly increased levels of lactate dehydrogenase (LDH). Complement-mediated HUS is considered genetic when 2 or more members of the same family are affected by the disease at least 6 months apart and exposure to a common triggering infectious agent has been excluded, or when pathogenic variants are identified in 1 or more of the genes known to be associated with aHUS, irrespective of familial history. A patient may have both autoantibodies to complement alternate pathway proteins and genetic defects in these genes. It is important to note that certain genetic defects in these genes, eg, complement C3 (C3), may be associated with a more classic immunodeficiency phenotype with recurrent infections with encapsulated pathogens and connective tissue diseases with no evidence of aHUS/TMA. Table 1. Genes included in the Complement aHUS/TMA PID Gene Panel

<table>
<thead>
<tr>
<th>GENE SYMBOL (ALIAS)</th>
<th>PROTEIN</th>
<th>OMIM</th>
<th>INCIDENCE</th>
<th>INHERITANCE</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS13</td>
<td>Protein</td>
<td>120700</td>
<td>Approximately 5%</td>
<td>AD, AR</td>
<td>Complement factor C3 deficiency (AR), susceptibility to aHUS (AD)</td>
</tr>
<tr>
<td>C3</td>
<td>Protein</td>
<td>604134</td>
<td>Not available</td>
<td>AR</td>
<td>Familial thrombotic thrombocytopenic purpura (TTP)</td>
</tr>
<tr>
<td>CFB</td>
<td>Protein</td>
<td>138470</td>
<td>Approximately 12%</td>
<td>AD, AR</td>
<td>Susceptibility to aHUS 2 CFB</td>
</tr>
<tr>
<td>CFH</td>
<td>Protein</td>
<td>138470</td>
<td>Approximately 12%</td>
<td>AD, AR</td>
<td>Susceptibility to aHUS 2 CFB</td>
</tr>
<tr>
<td>CFHR1</td>
<td>Protein</td>
<td>138470</td>
<td>Approximately 12%</td>
<td>AD, AR</td>
<td>Susceptibility to aHUS 2 CFB</td>
</tr>
<tr>
<td>CFHR3</td>
<td>Protein</td>
<td>138470</td>
<td>Approximately 12%</td>
<td>AD, AR</td>
<td>Susceptibility to aHUS 2 CFB</td>
</tr>
</tbody>
</table>

Table 1. Genes included in the Complement aHUS/TMA PID Gene Panel
**protein 3 isoform 1 precursor 605336 Rare AD, AR Susceptibility to aHUS**

**CFHR5 Complement factor H-related protein 5 precursor 608593 3% of aHUS AD Nephropathy due to CFHR5 deficiency**

**CFI Complement factor I isoform 2 preproprotein 217030 4%-10% of aHUS AD, AR Complement factor I deficiency (AR), susceptibility to aHUS (AD)**

**DGKE Diacylglycerol kinase epsilon 601440 Rare AR Nephrotic syndrome Type 7, susceptibility to aHUS**

**PLG Plasminogen isoform 1 precursor 173350 Rare AR Dysplasminogenemia, plasminogen deficiency**

**Type I THBD Thrombomodulin precursor 188040 Approximately 3%-5% of aHUS AD Thrombophilia due to thrombomodulin defect, susceptibility to aHUS**

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of complement-mediated HUS/atypical HUS (aHUS) or thrombotic microangiopathies (TMA) Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants in genes encoding complement alternate pathway components and specific coagulation pathway genes known to be associated with increased risk for aHUS/TMA allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CBC 9109**

**Complete Blood Count (CBC) with Differential, Blood**

**Clinical Information:** RBCs, WBCs, and platelets are produced in the bone marrow and released into the peripheral blood. The primary function of the RBC is to deliver oxygen to tissues. WBCs are key components of the immune system. Platelets play a vital role in blood clotting. Mean corpuscular volume (MCV) is a measure of the size of the average RBC. Anemias are characterized as microcytic (MCV <80), macrocytic (MCV >100), or normocytic. The red cell distribution width (RDW) is a measure of the degree of variation in RBC size (anisocytosis). RDW may be helpful in distinguishing between some anemias. For example, iron deficiency anemia is characterized by a high RDW, while thalassemia is characterized by a low RDW. These counts are used as clinical guides in the diagnosis or monitoring of many diseases.

**Useful For:** Screening tool to confirm a hematologic disorder, to establish or rule out a diagnosis, to detect an unsuspected hematologic disorder, or to monitor effects of radiation or chemotherapy

**Interpretation:** Results outside of normal value ranges may reflect a primary disorder of the cell-producing organs or an underlying disease. Results should be interpreted in conjunction with the patient's clinical picture and appropriate additional testing performed.
Reference Values:
RED BLOOD CELL COUNT (RBC)
Males:
0-14 days: 4.10-5.55 x 10(12)/L
15 days-4 weeks: 3.16-4.63 x 10(12)/L
5 weeks-7 weeks: 3.02-4.22 x 10(12)/L
8 weeks-5 months: 3.43-4.80 x 10(12)/L
6 months-23 months: 4.03-5.07 x 10(12)/L
24 months-35 months: 3.89-4.97 x 10(12)/L
3-5 years: 4.00-5.10 x 10(12)/L
6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.20-5.30 x 10(12)/L
15-17 years: 4.30-5.70 x 10(12)/L
Adults: 4.35-5.65 x 10(12)/L

Females:
0-14 days: 4.12-5.74 x 10(12)/L
15 days-4 weeks: 3.32-4.80 x 10(12)/L
5 weeks-7 weeks: 2.93-3.87 x 10(12)/L
8 weeks-5 months: 3.45-4.75 x 10(12)/L
6 months-23 months: 3.97-5.01 x 10(12)/L
24 months-35 months: 3.84-4.92 x 10(12)/L
3-5 years: 4.00-5.10 x 10(12)/L
6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.10-5.10 x 10(12)/L
15-17 years: 3.80-5.00 x 10(12)/L
Adults: 3.92-5.13 x 10(12)/L

HEMOGLOBIN
Males:
0-14 days: 13.9-19.1 g/dL
15 days-4 weeks: 10.0-15.3 g/dL
5 weeks-7 weeks: 8.9-12.7 g/dL
8 weeks-5 months: 9.6-12.4 g/dL
6 months-23 months: 10.1-12.5 g/dL
24 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-14 years: 12.4-15.7 g/dL
15-17 years: 13.3-16.9 g/dL
Adults: 13.2-16.6 g/dL

Females:
0-14 days: 13.4-20.0 g/dL
15 days-4 weeks: 10.8-14.6 g/dL
5 weeks-7 weeks: 9.2-11.4 g/dL
8 weeks-5 months: 9.9-12.4 g/dL
6 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-14 years: 12.4-15.7 g/dL
15-17 years: 13.3-16.9 g/dL
Adults: 11.6-15.0 g/dL

HEMATOCRIT
Males:
0-14 days: 39.8-53.6%

Females:
0-14 days: 39.8-53.6%
MEAN CORPUSCULAR VOLUME (MCV)
Males:
0-14 days: 91.3-103.1 fL
15 days-4 weeks: 89.4-99.7 fL
5 weeks-7 weeks: 84.3-94.2 fL
8 weeks-5 months: 74.1-87.5 fL
6 months-23 months: 69.5-87.5 fL
24 months-35 months: 71.3-84.0 fL
3-5 years: 77.2-89.5 fL
6-11 years: 77.8-91.1 fL
12-14 years: 79.9-93.0 fL
15-17 years: 82.5-98.0 fL
Adults: 78.2-97.9 fL

Females:
0-14 days: 92.7-106.4 fL
15 days-4 weeks: 90.1-103.0 fL
5 weeks-7 weeks: 83.4-96.4 fL
8 weeks-5 months: 74.8-88.3 fL
6 months-23 months: 71.3-82.6 fL
24 months-35 months: 72.3-85.0 fL
3-5 years: 77.2-89.5 fL
6-11 years: 77.8-91.1 fL
12-14 years: 79.9-93.0 fL
15-17 years: 82.5-98.0 fL
Adults: 78.2-97.9 3 fL

RED CELL DISTRIBUTION WIDTH (RDW)
Males:
0-14 days: 14.8-17.0%
15 days-4 weeks: 14.3-16.8%
5 weeks-7 weeks: 13.8-16.1%
8 weeks-5 months: 12.4-15.3%
6 months-23 months: 12.9-15.6%
24 months-35 months: 12.5-14.9%
3-5 years: 11.3-13.4%
6-17 years: 11.4-13.5%
Adults: 11.8-14.5%

Females:
0-14 days: 14.6-17.3%
15 days-4 weeks: 14.4-16.2%
5 weeks-7 weeks: 13.6-15.8%
8 weeks-5 months: 12.2-14.3%
6 months-23 months: 12.7-15.1%
24 months-35 months: 12.4-14.9%
3-5 years: 11.3-13.4%
6-17 years: 11.4-13.5%
Adults: 12.2-16.1%

WHITE BLOOD CELL COUNT (WBC)

Males:
0-14 days: 8.0-15.4 x 10^9/L
15 days-4 weeks: 7.8-15.9 x 10^9/L
5 weeks-7 weeks: 8.1-15.0 x 10^9/L
8 weeks-5 months: 6.5-13.3 x 10^9/L
6 months-23 months: 6.0-13.5 x 10^9/L
24 months-35 months: 5.1-13.4 x 10^9/L
3-5 years: 4.4-12.9 x 10^9/L
6-17 years: 3.8-10.4 x 10^9/L
Adults: 3.4-9.6 x 10^9/L

Females:
0-14 days: 8.2-14.6 x 10^9/L
15 days-4 weeks: 8.4-14.4 x 10^9/L
5 weeks-7 weeks: 7.1-14.7 x 10^9/L
8 weeks-5 months: 6.0-13.3 x 10^9/L
6 months-23 months: 6.5-13.0 x 10^9/L
24 months-35 months: 4.9-13.2 x 10^9/L
3-5 years: 4.4-12.9 x 10^9/L
6-17 years: 3.8-10.4 x 10^9/L
Adults: 3.4-9.6 x 10^9/L

PLATELETS

Males:
0-14 days: 218-419 x 10^9/L
15 days-4 weeks: 248-586 x 10^9/L
5 weeks-7 weeks: 229-562 x 10^9/L
8 weeks-5 months: 244-529 x 10^9/L
6 months-23 months: 206-445 x 10^9/L
24 months-35 months: 202-403 x 10^9/L
3-5 years: 187-445 x 10^9/L
6-9 years: 187-400 x 10^9/L
10-13 years: 177-381 x 10^9/L
14-17 years: 139-320 x 10^9/L
Adults: 135-317 x 10^9/L

Females:
0-14 days: 144-449 x 10^9/L
15 days-4 weeks: 279-571 x 10^9/L
5 weeks-7 weeks: 331-597 x 10^9/L
8 weeks-5 months: 247-580 x 10^9/L
6 months-23 months: 214-459 x 10^9/L
24 months-35 months: 189-394 x 10^9/L
### NEUTROPHILS

**Males:**
- 0-14 days: 1.60-6.06 x 10^9/L
- 15 days-4 weeks: 1.18-5.45 x 10^9/L
- 5 weeks-7 weeks: 0.83-4.23 x 10^9/L
- 8 weeks-5 months: 0.97-5.45 x 10^9/L
- 6 months-23 months: 1.19-7.21 x 10^9/L
- 24 months-35 months: 1.54-7.92 x 10^9/L
- 3-5 years: 1.60-7.80 x 10^9/L
- 6-16 years: 1.40-6.10 x 10^9/L
- 17 years: 1.80-7.20 x 10^9/L
- Adults: 1.56-6.45 x 10^9/L

**Females:**
- 0-14 days: 1.73-6.75 x 10^9/L
- 15 days-4 weeks: 1.23-4.80 x 10^9/L
- 5 weeks-7 weeks: 1.00-4.68 x 10^9/L
- 8 weeks-5 months: 1.04-7.20 x 10^9/L
- 6 months-23 months: 1.27-7.18 x 10^9/L
- 24 months-35 months: 1.60-8.29 x 10^9/L
- 3-5 years: 1.60-7.80 x 10^9/L
- 6-14 years: 1.50-6.50 x 10^9/L
- 15-17 years: 2.00-7.40 x 10^9/L
- Adults: 1.56-6.45 x 10^9/L

### LYMPHOCYTES

**Males:**
- 0-14 days: 2.07-7.53 x 10^9/L
- 15 days-4 weeks: 2.11-8.38 x 10^9/L
- 5 weeks-7 weeks: 2.47-7.95 x 10^9/L
- 8 weeks-5 months: 2.45-8.89 x 10^9/L
- 6 months-23 months: 1.56-7.83 x 10^9/L
- 24 months-35 months: 1.13-5.52 x 10^9/L
- 3-5 years: 1.60-5.30 x 10^9/L
- 6-11 years: 1.40-3.90 x 10^9/L
- 12-17 years: 1.00-3.20 x 10^9/L
- Adults: 0.95-3.07 x 10^9/L

**Females:**
- 0-14 days: 1.75-8.00 x 10^9/L
- 15 days-4 weeks: 2.42-8.20 x 10^9/L
- 5 weeks-7 weeks: 2.29-9.14 x 10^9/L
- 8 weeks-5 months: 2.14-8.99 x 10^9/L
- 6 months-23 months: 1.52-8.09 x 10^9/L
- 24 months-35 months: 1.25-5.77 x 10^9/L
- 3-5 years: 1.60-5.30 x 10^9/L
- 6-11 years: 1.40-3.90 x 10^9/L
- 12-17 years: 1.00-3.20 x 10^9/L
- Adults: 0.95-3.07 x 10^9/L

### MONOCYTES

**Males:**
- 3-5 years: 187-445 x 10^9/L
- 6-9 years: 187-400 x 10^9/L
- 10-13 years: 177-381 x 10^9/L
- 14-17 years: 158-362 x 10^9/L
- Adults: 157-371 x 10^9/L

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0-14 days: 0.52-1.77 x 10(9)/L
15 days-4 weeks: 0.28-1.38 x 10(9)/L
5 weeks-7 weeks: 0.28-1.05 x 10(9)/L
8 weeks-5 months: 0.28-1.07 x 10(9)/L
6 months-23 months: 0.25-1.15 x 10(9)/L
24 months-35 months: 0.19-0.94 x 10(9)/L
3-5 years: 0.30-0.90 x 10(9)/L
6-17 years: 0.20-0.80 x 10(9)/L
Adults: 0.26-0.81 x 10(9)/L

Females:
0-14 days: 0.57-1.72 x 10(9)/L
15 days-4 weeks: 0.42-1.21 x 10(9)/L
5 weeks-7 weeks: 0.28-1.21 x 10(9)/L
8 weeks-5 months: 0.24-1.17 x 10(9)/L
6 months-23 months: 0.26-1.08 x 10(9)/L
24 months-35 months: 0.24-0.92 x 10(9)/L
3-5 years: 0.30-0.90 x 10(9)/L
6-17 years: 0.20-0.80 x 10(9)/L
Adults: 0.26-0.81 x 10(9)/L

EOSINOPHILS
Males:
0-14 days: 0.12-0.66 x 10(9)/L
15 days-4 weeks: 0.08-0.80 x 10(9)/L
5 weeks-7 weeks: 0.05-0.57 x 10(9)/L
8 weeks-5 months: 0.03-0.61 x 10(9)/L
6 months-23 months: 0.02-0.82 x 10(9)/L
24 months-35 months: 0.03-0.53 x 10(9)/L
3-11 years: 0.00-0.50 x 10(9)/L
12-17 years: 0.10-0.20 x 10(9)/L
Adults: 0.03-0.48 x 10(9)/L

Females:
0-14 days: 0.09-0.64 x 10(9)/L
15 days-4 weeks: 0.06-0.75 x 10(9)/L
5 weeks-7 weeks: 0.04-0.63 x 10(9)/L
8 weeks-5 months: 0.02-0.74 x 10(9)/L
6 months-23 months: 0.02-0.58 x 10(9)/L
24 months-35 months: 0.03-0.46 x 10(9)/L
3-11 years: 0.00-0.50 x 10(9)/L
12-17 years: 0.10-0.20 x 10(9)/L
Adults: 0.03-0.48 x 10(9)/L

BASOPHILS
Males:
0-14 days: 0.02-0.11 x 10(9)/L
15 days-7 weeks: 0.01-0.07 x 10(9)/L
8 weeks-35 months: 0.01-0.06 x 10(9)/L
3-17 years: 0.00-0.10 x 10(9)/L
Adults: 0.01-0.08 x 10(9)/L

Females:
0-14 days: 0.02-0.07 x 10(9)/L
15 days-4 weeks: 0.01-0.06 x 10(9)/L
5 weeks-7 weeks: 0.01-0.05 x 10(9)/L
8 weeks-5 months: 0.01-0.07 x 10(9)/L
6 months-35 months: 0.01-0.06 x 10(9)/L
3-17 years: $0.00-0.10 \times 10^{9}/L$
Adults: $0.01-0.08 \times 10^{9}/L$


**Comprehensive Cardiomyopathy Multi-Gene Panel, Blood**

**Clinical Information:** The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other causes, such as structural abnormalities, systemic hypertension, or physiologic hypertrophy due to rigorous athletic training (athlete’s heart). The incidence of HCM in the general population is approximately 1 in 500, and the hereditary form is most often caused by variants in genes encoding the components of the cardiac sarcomere. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can also cause life-threatening arrhythmias that increase the risk of sudden cardiac death. DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias or conduction system disease, or thromboembolic disease (stroke). The incidence of DCM is likely higher than originally reported due to subclinical phenotypes and underdiagnosis, with recent estimates suggesting that DCM affects approximately 1 in every 250 people. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as “idiopathic” dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. Arrhythmogenic right ventricular dysplasia (ARVD or AC) is characterized by breakdown of the myocardium and replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. Age of onset and severity are variable, but symptoms typically develop in adulthood. The incidence of ARVC is approximately 1 in 1,000 to 1 in 2,500. LVNC is characterized by left ventricular hypertrophy and prominent trabeculations of the ventricular wall, giving a spongy appearance to the muscle wall. It is thought to be caused by the arrest of normal myocardial morphogenesis. Clinical presentation is highly variable, ranging from no symptoms to congestive heart failure and life-threatening arrhythmias. An increased risk of thromboembolic events is also present with LVNC. Approximately 67% of LVNC is considered familial. Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy and is associated with abnormally rigid ventricular walls. Systolic function can be normal or near normal, but diastolic dysfunction is present. There are several nongenetic causes of RCM, but this condition can be familial as well, with the TNNI3 gene accounting for the majority of inherited cases. The age at presentation for familial RCM ranges from childhood to adulthood, and there is an increased risk of sudden death associated with this condition. Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, and characteristic facial dysmorphism. HCM is present in approximately 20% to 30% of individuals affected with NS. There are a number of disorders with significant phenotypic overlap with NS, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). NS and related disorders (also called the RASopathies) are caused by variants in genes involved in the RAS-MAPK signaling pathway. In some cases, variants in these genes may cause cardiomyopathy in the absence of other syndromic features. Cardiomyopathy may also be caused by an underlying systemic disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic
storage disorder. In these cases, cardiomyopathy may be the first feature to come to attention clinically.

The hereditary forms of cardiomyopathy are most frequently associated with an autosomal dominant form of inheritance; however, X-linked and autosomal recessive forms of disease are also present. In some cases, compound heterozygous or homozygous variants may be present in genes typically associated with autosomal dominant inheritance, often leading to a more severe phenotype. Digenic variants (2 different heterozygous variants at separate genetic loci) in autosomal dominant genes have also been reported to occur in patients with severe disease (particularly HCM and ARVC). The inherited cardiomyopathies display both allelic and locus heterogeneity, whereby a single gene may cause different forms of cardiomyopathy (allelic heterogeneity) and variants in different genes can cause the same form of cardiomyopathy (locus heterogeneity).

This comprehensive cardiomyopathy panel includes sequence analysis of 55 genes and may be considered for individuals with HCM, DCM, ARVC, or LVNC, whom have had uninformative test results from a more targeted, disease-specific test. This test may also be helpful when the clinical diagnosis is not clear, or when there is more than 1 form of cardiomyopathy in the family history. It is important to note that the number of variants of uncertain significance detected by this panel may be higher than for the disease-specific panels, making clinical correlation more difficult.

Genes included in the Comprehensive Cardiomyopathy Multi-Gene Panel Gene Inheritance Disease Association ABC9 ATP-binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKR1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM BRAF V-RAF murine sarcoma viral oncogene homolog B1 AD Noonan/CFC/Costello syndrome CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tatyama-type distal myopathy, rippling muscle disease CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder CRYAB Crystalisin, alpha-B AD, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD DSC2 Desmocollin AD, AR ARVC, ARVC + skin and hair findings DSG2 Desmoglein AD ARVC DSP Desmoplakin AD, AR DCM, Carvalj syndrome DTNA Dystrobrevin, alpha AD LVNC, CHD GLA Galactosidase, alpha X-linked Fabry disease HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome JUP Junction plakoglobin AD, AR ARVC, Naxos disease KRAS V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome LAMA4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated member protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC MYBPC3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH6 Myosin, heavy chain 6, cardiac muscle, alpha HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light cahin 2, regulatory, cardiac, slow AD HCM MYL3 Myosin, light chain 3, alkali, ventricular, skeletal, slow AD, AR ARVC MYLK2 Myosin light chain kinase 2 AD HCM MYOZ2 Myozenin 2 AD HCM MYPN Myopalladin AD HCM, DCM NEXN Nexilin AD HCM, DCM NRAS Neuroblastoma RAS viral oncogene homolog AD Noonan syndrome PKP2 Plakophilin 2 AD ARVC PLN Phospholamban AD HCM, DCM PRKAG2 Protein kinase, AMP-activated, noncatalytic, gamma2 AD HCM, Wolff-Parkinson-White syndrome PTEN11 Proetin-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/multiple lentigines syndrome RAFl V-RAF-1 murine leukemia viral oncogene homolog 1 AD Noonan/multiple lentigines syndrome RBM20 RNA-binding motif protein 20 AD DCM RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS SCN5A Sodium channel, voltage gated, type V, alpha subunit AD Brugada syndrome, DCM, Heart block, LQTS, SSS, SIDS SGCD Sarcoglycan, delta AD, AR DCM, LGMD SHOC2 Suppressor of clear, C. elegans, homolog of AD Noonan syndrome-like with loose anagen hair Son1 of sevenless, dropshophil, homolog 1 AD Noonan syndrome TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TAP1 Titin-cap (telethonin) AD, AR HCM, DCM, LGMD TMEM43 Transmembrane protein 43 AD ARVC, EMD TNRC6 C Troponin C, slow AD HCM, DCM TNNT1 Troponin I, cardiac AD, AR DCM, HCM, RCM TNNT2 Troponin T2, cardiac AD HCM, DCM, LVNC TPM1 Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, ARVC, myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arhythmicogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emery muscular dystrophy (EMD), congenital heart defect (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive
**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary cardiomyopathy. Establishing a diagnosis of a hereditary cardiomyopathy and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved. Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members.

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**G109** 65824

**Comprehensive CDG Panel (Bill Only)**

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

**FCDUC** 75472

**Comprehensive Drug Screen, Umbilical Cord Tissue**

**Reference Values:**
Reporting limit(s) determined each analysis.
None Detected ng/g

**CMAMA** 113631

**Comprehensive Metabolic Panel, Serum**

**Clinical Information:** The comprehensive metabolic panel measures 14 analytes and calculates an
anion gap. It is used to assess kidney or liver status, electrolyte and acid/base balance, and blood glucose. This comprehensive metabolic panel can also provide information about a patient's response to medications that would impact kidney or liver function.

**Useful For:** Routine health monitoring Patient monitoring while hospitalized for information regarding metabolism, including the current kidney status, electrolyte and acid/base balance, and blood glucose.

**Interpretation:** Comprehensive metabolic panel results are usually evaluated in conjunction with each other for patterns of results. The pattern of abnormal results can help identify the possible conditions or diseases present. Many conditions will cause abnormal results including kidney failure, breathing problems, and diabetes-related complications.

**Reference Values:**

**SODIUM**
- <1 year: not established
- ≥1 year: 135-145 mmol/L

**POTASSIUM**
- <1 year: not established
- ≥1 year: 3.6-5.2 mmol/L

**CHLORIDE**
- <1 year: not established
- 1-17 years: 102-112 mmol/L
- ≥18 years: 98-107 mmol/L

**BICARBONATE**
- Males:
  - <1 year: not established
  - 1-2 years: 17-25 mmol/L
  - 3 years: 18-26 mmol/L
  - 4-5 years: 19-27 mmol/L
  - 6-7 years: 20-28 mmol/L
  - 8-17 years: 21-29 mmol/L
  - ≥18 years: 22-29 mmol/L
- Females:
  - <1 year: not established
  - 1-3 years: 18-25 mmol/L
  - 4-5 years: 19-26 mmol/L
  - 6-7 years: 20-27 mmol/L
  - 8-9 years: 21-28 mmol/L
  - ≥10 years: 22-29 mmol/L

**ANION GAP**
- <7 years: not established
- ≥7 years: 7-15

**BLOOD UREA NITROGEN (BUN)**
- Males:
  - <12 months: not established
  - 1-17 years: 7-20 mg/dL
  - ≥18 years: 8-24 mg/dL
- Females:
  - <12 months: not established
  - 1-17 years: 7-20 mg/dL
  - ≥18 years: 6-21 mg/dL
CREATININE
Males:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)
>60 mL/min/BSA
Estimated GFR calculated using the 2009 CKD_EPI creatinine equation

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: not established
> or =1 year: 70-140 mg/dL

TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are <12 months of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are <12 months of age.

ASPARTATE AMINOTRANSFERASE (AST)
Males:
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females:
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

ALKALINE PHOSPHATASE (ALP)
Males:
4 years: 149-369 U/L
5 years: 179-416 U/L
6 years: 179-417 U/L
7 years: 172-405 U/L
8 years: 169-401 U/L
9 years: 175-411 U/L
ALANINE AMINOTRANSFERASE (ALT)

Males:
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are <12 months of age.

Females:
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are <12 months of age.

TOTAL BILIRUBIN
0-6 days: Refer to http://biltool.org/ for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: <15.0 mg/dL.
15 days to 17 years: < or =0.9 mg/dL.
>18 years: < or =1.2 mg/dL.

Congenital Adrenal Hyperplasia (CAH) Pediatric Profile 6, Comprehensive Screen

Interpretation:

Reference Values:

Androstenedione
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>63 - 935</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>50 - 449</td>
</tr>
<tr>
<td>Full Term (1-7 days)</td>
<td>279</td>
</tr>
</tbody>
</table>

Levels decrease rapidly to after one week.

1 - 11m 37

Androstenedione gradually decreases during the first six months to prepubertal levels.

Prepubertal Children 17
Adult Males 44 - 186
Adult Females 28 - 230
Females Postmenopausal
Cortisol
Units: ug/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>1.0 - 11</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>2.5 - 9.1</td>
</tr>
<tr>
<td>Full Term Day 3</td>
<td>1.7 - 14</td>
</tr>
<tr>
<td>Full Term Day 7</td>
<td>2.0 - 11</td>
</tr>
<tr>
<td>31d - 11m</td>
<td>2.8 - 23</td>
</tr>
<tr>
<td>12m - 15y (8:00 AM)</td>
<td>3.0 - 21</td>
</tr>
</tbody>
</table>

Adults
8:00 AM 8.0 - 19
4:00 PM 4.0 - 11

Deoxycorticosterone (DOC)

Units: ng/dL
Newborn: Levels are markedly elevated at birth and decrease rapidly during the first week to the range of 7 - 49 as found in older infants.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 28w) Day 4</td>
<td>20 - 105</td>
</tr>
<tr>
<td>Premature (34 - 36w) Day 4</td>
<td>28 - 78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 11m</td>
<td>7 - 49</td>
</tr>
<tr>
<td>Prepubertal Children</td>
<td>2 - 34</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>2 - 19</td>
</tr>
</tbody>
</table>

Dehydroepiandrosterone (DHEA)

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 31w)</td>
<td>82 - 1484</td>
</tr>
<tr>
<td>Premature (32 - 35w)</td>
<td>56 - 1853</td>
</tr>
<tr>
<td>Full Term (2 - 7d)</td>
<td>41 - 1292</td>
</tr>
<tr>
<td>8d - 5m</td>
<td></td>
</tr>
<tr>
<td>6 - 12m</td>
<td></td>
</tr>
<tr>
<td>1 - 5 y</td>
<td></td>
</tr>
<tr>
<td>6 - 7 y</td>
<td></td>
</tr>
<tr>
<td>8 - 10 y</td>
<td></td>
</tr>
<tr>
<td>11 - 12 y</td>
<td></td>
</tr>
<tr>
<td>13 - 14 y</td>
<td></td>
</tr>
<tr>
<td>15 - 16 y</td>
<td>39 - 481</td>
</tr>
<tr>
<td>17 - 19 y</td>
<td>40 - 491</td>
</tr>
<tr>
<td>20 - 49 y</td>
<td>31 - 701</td>
</tr>
<tr>
<td>&gt; or = 50 y</td>
<td>21 - 402</td>
</tr>
</tbody>
</table>

11-Desoxycortisol

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>110 - 1376</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>48 - 579</td>
</tr>
<tr>
<td>Newborn Day 3</td>
<td>13 - 147</td>
</tr>
<tr>
<td>1 - 11m</td>
<td>156</td>
</tr>
<tr>
<td>Prepubertal 8:00 AM</td>
<td>20 - 155</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>12 - 158</td>
</tr>
</tbody>
</table>

17-OH Pregnenolone

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
</table>
Premature (26-28w) Day 4  375 - 3559
Premature (31-35w) Day 4  64 - 2380
3 Days                  10 - 829
1 - 5m                  36 - 763
6 - 11m                 42 - 540
12 - 23m                14 - 207
24m - 5y                10 - 103
6 - 9y                  10 - 186
Pubertal                44 - 235
Adults                  53 - 357

Progesterone
Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>1 - 16y</td>
<td>15</td>
</tr>
<tr>
<td>Adults</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>1-10y</td>
<td>26</td>
</tr>
<tr>
<td>11y</td>
<td>255</td>
</tr>
<tr>
<td>12y</td>
<td>856</td>
</tr>
<tr>
<td>13y</td>
<td>693</td>
</tr>
<tr>
<td>14y</td>
<td>1204</td>
</tr>
<tr>
<td>15y</td>
<td>1076</td>
</tr>
<tr>
<td>16y</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>Cycle Days</td>
<td></td>
</tr>
<tr>
<td>1 - 6</td>
<td>17</td>
</tr>
<tr>
<td>7 - 12</td>
<td>135</td>
</tr>
<tr>
<td>13 - 15</td>
<td>1563</td>
</tr>
<tr>
<td>16 - 28</td>
<td>2555</td>
</tr>
</tbody>
</table>

Post Menopausal

Note: Luteal progesterone peaked from 350 to 3750 ng/dL on days ranging from 17 to 23.

17-Alpha-Hydroxyprogesterone 17-OHP
Units: ng/dL
### Testosterone, Total

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>124 - 841</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>26 - 568</td>
</tr>
<tr>
<td>Full-Term Day 3</td>
<td></td>
</tr>
</tbody>
</table>

Males: Levels increase after the first week to peak values ranging from 40 - 200 between 30 and 60 days. Values then decline to a prepubertal value of one year.

**Prepubertal**

**Adult Males**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>1 - 11m</td>
<td>13 - 106</td>
</tr>
</tbody>
</table>

**Prepubertal**

**Adult Females**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>15-70</td>
</tr>
<tr>
<td>Luteal</td>
<td>35-290</td>
</tr>
</tbody>
</table>

### Testosterone, Total

<table>
<thead>
<tr>
<th>Units: ng/dL</th>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>59 - 125</td>
<td></td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>37 - 198</td>
<td></td>
</tr>
<tr>
<td>Newborns</td>
<td>75 - 400</td>
<td></td>
</tr>
</tbody>
</table>

**1 - 7m:** Levels decrease rapidly the first week to 20 - 50, then increase to 60 - 400 between 20 - 60 days. Levels then decline to prepubertal range levels of 10 by seven months.

**Females**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 28w) Day 4</td>
<td>5 - 16</td>
</tr>
<tr>
<td>Premature (31 - 35w) Day 4</td>
<td>5 - 22</td>
</tr>
<tr>
<td>Newborns</td>
<td>20 - 64</td>
</tr>
</tbody>
</table>

**1 - 7m:** Levels decrease during the first month to less than 10 and remain there until puberty.

**Prepubertal Males and Females**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>10</td>
</tr>
<tr>
<td>Adult Males &gt;18 years</td>
<td>264 - 916</td>
</tr>
</tbody>
</table>

**Premenopausal**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Females</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>10 - 55</td>
</tr>
</tbody>
</table>
## Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency, Serum

**Clinical Information:** The cause of congenital adrenal hyperplasia (CAH) is an inherited genetic defect that results in decreased formation of 1 of the many enzymes that are involved in the production of cortisol. The enzyme defect results in reduced glucocorticoids and mineralocorticoids, and elevated 17-hydroxyprogesterone (OHPG) and androgens. The resulting hormone imbalances can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. Adult-onset CAH may result in hirsutism or infertility in females. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 positions to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and the feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequently, increased pituitary release of ACTH increases production of OHPG. In contrast, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-ol-dehydrogenase (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone, respectively. Most (90%) cases of CAH are due to mutations in the 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione with decreased cortisol. By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (DCRN / 11-Deoxycorticosterone, Serum), respectively, are necessary for diagnosis. OHPG is bound to both transcortin and albumin, and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests than pregnanetriol measurement are available to diagnose disorders of steroid metabolism. The CAH profile allows the simultaneous determination of OHPG, androstenedione, and cortisol. These steroids can also be ordered individually (OHPG / 17-Hydroxyprogesterone, Serum; ANST / Androstenedione, Serum; CINP / Cortisol, Serum, LC-MS/MS).

### Postmenopausal

<table>
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<tr>
<th>Tanner Stage</th>
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<th>Male</th>
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<tr>
<td>2</td>
<td>9.8 - 14.5</td>
<td>18 - 150</td>
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<td>3</td>
<td>10.7 - 15.4</td>
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<td>4</td>
<td>11.8 - 16.2</td>
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### Males

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<td>4</td>
<td>10.7 - 15.6</td>
<td>13 - 32</td>
</tr>
<tr>
<td>5</td>
<td>11.8 - 18.6</td>
<td>20 - 38</td>
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</table>

### Females
**Useful For:** Preferred screening test for congenital adrenal hyperplasia (CAH) that is caused by 21-hydroxylase deficiency Part of a battery of tests to evaluate females with hirsutism or infertility, which can result from adult-onset CAH

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-Hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common is 3 beta-hydroxysteroid dehydrogenase type 2 (3 beta HSD-2) deficiency, characterized by low cortisol and substantial elevations in dehydroepiandrosterone sulfate (DHEA-S) and 17-alpha-hydroxyprogrenenolone, while androstenedione is either low, normal, or rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare steroidogenic acute regulatory protein deficiency, all steroid hormone levels are low and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoïd and its precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxy corticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. OHPG is measured to guide treatment, but this test correlates only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable.

**Reference Values:**

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<th>Reference Range (ng/dL)</th>
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<td>Stage II</td>
<td>9.8-14.5</td>
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<td>Stage III</td>
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<td>Stage IV</td>
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<td>Stage V</td>
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<td>65-210 Females*</td>
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<table>
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<th>Tanner Stages</th>
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<th>Reference Range (ng/dL)</th>
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</thead>
<tbody>
<tr>
<td>Stage I (prepubertal)</td>
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<td></td>
</tr>
<tr>
<td>Stage II</td>
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</tr>
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<td>Stage III</td>
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<tr>
<td>Stage IV</td>
<td>10.7-15.6</td>
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</table>
<15.1 ng/mL

ANDROSTENEDIONE
<3.1 ng/mL

CORTISOL
Not applicable

11-DEOXYCORTISOL
<15.1 ng/mL

21-DEOXYCORTISOL
<4.1 ng/mL

(17 OHP + ANDROSTENEDIONE)/CORTISOL RATIO
<1.1
Note: Abnormal (17 OHP + Androstenedione)/Cortisol Ratio: > or =1.1 is only applicable when 17-OHP is elevated

11-DEOXYCORTISOL/CORTISOL RATIO
Not applicable

Clinical References:

CDGGP
608010

Congenital Disorders of Glycosylation Gene Panel, Varies

Clinical Information:
Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of disorders affecting several steps of the pathway involved in the glycosylation of proteins. CDG are classified into 5 groups. CDG types I and II will have abnormal biochemical findings detected by serum transferrin and serum total N-glycan analyses (see CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum). In the other 3 groups these analyses will be normal. CDG type I disorders are characterized by defects in the assembly or transfer of the dolichol-linked glycan, while CDG type II includes defects of the glycan moiety processing. The third group includes disorders of glycosylphosphatidyl inositol (GPI) anchor protein glycosylation. If clinically suspected, a flow cytometry analysis could facilitate the diagnostic workup. The fourth group involves disorders of O-mannosylation, a process that takes place predominantly in the muscle and brain tissues. The fifth group involves deglycosylation defects (eg, NAGLY1-CDG). The urine oligosaccharide profile by matrix-assisted laser desorption/ionization time-of-flight/time-of-flight mass spectrometer (MALDI-TOF/TOF-MS) may be abnormal and facilitate the diagnostic workup. CDG typically present as multisystemic disorders with a broad range of clinical features including developmental delay, hypotonia, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases, ranging from hydrops fetalis to a mild presentation in adults. Almost all types of CDG are autosomal recessive in inheritance, but some are X-linked. The broad clinical spectrum and genetic heterogeneity of CDG make a comprehensive panel a helpful tool in establishing a diagnosis for patients with suggestive clinical features.

Useful For:
Establishing a molecular diagnosis for patients with congenital disorders of glycosylation Identifying variants within genes known to be associated with congenital disorders of glycosylation, allowing for predictive testing of at-risk family members
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CDGN 65485**

**Congenital Disorders of N-Glycosylation, Serum**

**Clinical Information:** Congenital disorders of glycosylation (CDG) are a group of over 100 inherited metabolic disorders affecting largely N- and O-glycosylation of proteins. Almost 50 inborn errors of metabolism are attributed to congenital defects in N-glycosylation, which takes place primarily in the cytoplasm and in the membranes of the endoplasmic reticulum. O-glycosylation defects are commonly tissue specific and present differently than classic N-linked defects. CDG are currently classified into 2 main groups. Type I CDG is characterized by defects in the assembly or transfer of the dolichol-linked glycan (sugar chain), while type II involves processing defects of the glycan. Depending on the specific defect, an N-glycosylation disorder can be either a type I or type II CDG. N-linked CDG are phenotypically diverse, commonly presenting as clinical syndromes with multisystemic involvement and a broad clinical spectrum. There is considerable variation in the severity of this group of diseases ranging from a mild presentation in adults to severe multi-organ dysfunction causing infantile lethality. Intellectual disability is common, although in some subtypes, phosphomannose isomerase (MPI)-CDG (CDG-Ib) in particular, this is not observed. CDG should be considered in all patients with multisystem disease and in those with neurologic abnormalities including developmental delay and seizures, brain abnormalities such as cerebellar atrophy or hypoplasia as well as unexplained liver dysfunction. Additional common symptoms that may or may not be present include abnormal subcutaneous fat distribution, gastrointestinal issues such as vomiting, chronic diarrhea, and protein-losing enteropathy, eye abnormalities including retinal degeneration and strabismus, and cardiomyopathy. Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) analysis of released N-linked oligosaccharides, as is performed in this assay, is a global assessment of N-linked glycosylation. This complements the also performed transferrin and apolipoprotein CIII isoform analysis (see CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum) by providing additional information on specific structural oligosaccharide abnormalities that can in turn guide molecular testing.

**Useful For:** Screening for N-linked congenital disorders of glycosylation Providing information on specific structural oligosaccharide abnormalities to potentially direct further genetic testing

**Interpretation:** The results of the transferrin and apolipoprotein CIII isoform analysis are followed up with matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) analysis of released N-linked oligosaccharides to assess N-linked glycosylation. Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to more precisely identify the specific congenital disorder of glycosylation (CDG). Treatment options, the name and telephone number of contacts who may provide studies, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided.

**Reference Values:**
Interpretative comment only.

**Clinical References:**
NGCDA 64924

Congenital Dyserythropoietic Anemia Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This panel aids in the diagnosis and genetic counseling of individuals with clinical or familial features of congenital dyserythropoietic anemia (CDA). CDA is a disorder of ineffective erythropoiesis clinically subdivided into subtypes with various phenotypic findings that segregate into different gene associations.(1-4) These disorders have distinctive cytopathologic findings consisting of nuclear abnormalities in bone marrow erythroid precursors. Types I and II CDA are inherited in an autosomal recessive pattern whereas types III and IV are autosomal dominant.

Useful For: Confirmation of the diagnosis or carrier mutation status of genes associated with congenital dyserythropoietic anemia Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(5,6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


FIBNG 64867

Congenital Fibrinogen Disorders, FGA, FGB, and FGG Genes, Next-Generation Sequencing, Varies

Clinical Information: Fibrinogen forms the insoluble fibrin matrix that is a major component of the blood clots critical for stopping blood loss. Fibrinogen is made up of six polypeptide chains-one pair each of alpha, beta, and gamma chains (encoded by the FGA, FGB, and FGG genes respectively)-that are held together by 29 disulfide bonds.(2) The alpha, beta, and gamma fibrinogen subunits polymerize
to form an insoluble fibrin matrix that is a major component of the blood clots critical for stopping
blood loss. Fibrinogen also has a role in the early stages of wound repair. Fibrinogen disorders are
classified as either 1) afibrinogenemia or hypofibrinogenemia, a quantitative defect of low or absent
fibrinogen plasma antigen levels, or 2) dysfibrinogenemia or hypodysfibrinogenemia, a qualitative
defect in function and activity with normal or reduced antigen levels. Congenital afibrinogenemia and
hypofibrinogenemia are inherited in an autosomal recessive manner. Congenital dysfibrinogenemia is,
in most cases, inherited in an autosomal dominant manner but cases of recessive inheritance have also
been reported. Afibrinogenemia: Afibrinogenemia is characterized by the complete absence of
fibrinogen in circulation. Although all individuals with afibrinogenemia have unmeasurable functional
fibrinogen, the severity of bleeding is highly variable, even among those with the same genetic
alteration(s).(3) Abnormal bleeding may occur in the neonatal period as umbilical cord bleeding.
Bleeding may occur in skin, the oral cavity, gastrointestinal tract, genitourinary tract, or central nervous
system. Intracranial hemorrhage is a major cause of death in affected individuals, who are also at risk
for joint bleeds and spontaneous splenic rupture. Venous and arterial thromboembolic complications
and poor wound healing may also occur. Affected women have increased risk for menometrorrhagia
and recurrent pregnancy loss. The prevalence of afibrinogenemia is estimated to be 1 in 1 million.
Hypofibrinogenemia: Most individuals with hypofibrinogenemia (characterized by fibrinogen levels
less than 1.5 g/L) are asymptomatic.(3) Thromboembolism may occur spontaneously or with fibrinogen
substitution therapy. Affected individuals may experience abnormal bleeding after trauma or if they
have a second hemostatic abnormality. Recurrent pregnancy loss and postpartum hemorrhage are
reported in affected women. There is typically good correlation between fibrinogen levels and clinical
severity, with levels less than 0.5 g/L associated with major bleeding.(4) Specific alterations associated
with hypofibrinogenemia are strongly correlated with hepatic storage disease.(3) Acquired
hypofibrinogenemia has been reported in individuals with hepatic failure or decompensation cirrhosis.
Hypofibrinogenemia is also commonly associated with acute disseminated intravascular coagulation
(DIC). Less common acquired causes include administration of L-asparaginase and valproic acid or
other drugs that impair hepatic synthesis. These causes of acquired hypofibrinogenemia should be
excluded prior to genetic testing for a fibrinogen disorder. Dysfibrinogenemia and
Hypodysfibrinogenemia: About half of individuals with dysfibrinogenemia and hypodysfibrinogenemia
are asymptomatic. However, alteration carriers carry a high risk of major bleeding and/or
thromboembolic complications.(5) Patients bleed most after trauma, surgery, or postpartum. Some
women have spontaneous abortions. Specific alterations associated with dysfibrinogenemia are strongly
associated with thromboembolic pulmonary hypertension and amyloidosis. Causes of acquired
(non-genetic) dysfibrinogenemia or defects in fibrinogen that should be excluded prior to genetic testing
include cirrhosis, acute or chronic hepatitis, metastatic hepatoma, renal carcinoma, and biliary
obstruction. Individuals treated with isotretinoin therapy have also been reported to develop acquired
dysfibrinogenemia. Fibrinogen antibodies and inhibitors have been reported in systemic lupus
erythematosus, ulcerative colitis, and multiple myeloma. These causes of acquired dysfibrinogenemia
and hypodysfibrinogenemia should be considered and excluded prior to genetic testing for a fibrinogen
disorder.

**Useful For:** Genetic confirmation of congenital disorders of fibrinogen with the identification of an
alteration in FGA, FGB, or FGG that is known or suspected to cause disease Testing for close family
members of an individual with a diagnosis of afibrinogenemia/hypofibrinogenemia or
dysfibrinogenemia/hypodysfibrinogenemia This test is not intended for prenatal diagnosis

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is
performed using the most recent published American College of Medical Genetics and Genomics
(ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance.
Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory,
or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in
complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**
An interpretive report will be provided

**Clinical References:** 1. Verhovsek M, Moffat KA, Hayward CP: Laboratory testing for fibrinogen

**CLADP 608019**

**Congenital Lactic Acidosis Panel, Varies**

**Clinical Information:** Congenital lactic acidosis (CLA) is a rare, but serious condition that presents in newborns with extreme elevations of lactic acid and is caused by a variety of biochemical disorders, resulting in impaired mitochondrial activity. Elevated lactate in multiple specimen types such as blood and cerebrospinal fluid (CSF) are typically observed. However, additional symptoms are extremely variable, as any high-energy organ or tissue may be impaired, resulting in a need for multisystem screening that may involve biopsies and biochemical analysis. CLA can be caused by pathogenic variants in genes encoding enzymes involved in gluconeogenesis, pyruvate oxidation, the Krebs cycle, and mitochondrial function. A comprehensive gene panel with mitochondrial genome analysis is an essential tool to establish a diagnosis for patients with congenital lactic acidosis. As biomarker testing and multisystem organ assessments are not specific and can yield complex results, genetic testing is required to distinguish among the spectrum of conditions that can cause CLA. This panel analyzes a combination of nuclear genes for single-gene biochemical disorders known to cause CLA, as well as analysis of the mitochondrial genome.

**Useful For:** Follow up for abnormal biochemical results suggestive of congenital lactic acidosis
Establishing a molecular diagnosis for patients with congenital lactic acidosis
Identifying variants within genes known to be associated with congenital lactic acidosis, allowing for predictive testing of at-risk family members

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

**Reference Values:**
An interpretive report will be provided.


**SCNGP 65669**

**Congenital Neutropenia, Primary Immunodeficiency Disorder Panel (18 genes), Next-Generation Sequencing, Varies**

**Clinical Information:** Severe congenital neutropenia is a primary immunodeficiency disorder (PIDD) that is characterized by severe and recurrent bacterial infections, such as otitis media, bronchitis, pneumonia, osteomyelitis, and cellulitis, typically with the absence of pus at the infected site. Susceptibility to fungal infections may also be observed. Neutropenia may be an isolated finding or may be part of a syndrome. This panel includes genes associated with neutropenia as a major presenting feature; other panels may be more appropriate when neutropenia is identified but not as the main finding. Pathogenic variants in ELANE, which encodes neutrophil elastase, can result in severe congenital neutropenia type 1 (SCN1) or cyclic neutropenia. SCN1 often presents immediately with omphalitis, while diarrhea, pneumonia, and deep abscesses affecting the liver, lungs, or subcutaneous
tissues are noted within the first year. Patients are at risk for development of myelodysplastic syndrome or acute myelogenous leukemia, presumably due to acquired mutations in CSF3R (which may also be identified in the presence of congenital neutropenia due to variants in genes other than ELANE, see below). Biallelic mutations in CSF3R have also been recently reported to be associated with severe congenital neutropenia. Cyclic neutropenia typically presents in the first year of life with 3-week-long oscillations in cell counts along with intervals of fever, oral ulcerations, and ulcerations; between intervals, patients are generally healthy. Unlike SCN1, cyclic neutropenia is not associated with risk of malignancy. Both SCN1 and cyclic neutropenia are inherited in an autosomal dominant pattern from an affected parent, although de novo variants have been identified. Studies have demonstrated pathogenic variants in ELANE in nearly 100% of cases with well-documented classical cyclic neutropenia, while in some cases with atypical presentations (ie, oscillations that are not 3 weeks) a variant in ELANE is not identified. ELANE variants are identified in 38% to 80% of cases of congenital neutropenia, depending on the criteria used to identify patients. Although there is some overlap, generally, variants at the active site of neutrophil elastase result in cyclic neutropenia, while variants that prevent normal folding or packaging of the enzyme cause congenital neutropenia. In addition to variants in ELANE, severe congenital neutropenia, where the predominant finding is neutropenia, can be inherited as a result of pathogenic variants in other genes. Dominant variants in GFI1 (encoding growth factor independent 1) result in severe congenital neutropenia type 2 (SCN2). Pathogenic variants in G6PC3 (encoding glucose-6-phosphate 3), which are inherited in an autosomal recessive manner, can result in a phenotypic spectrum from isolated/nonsyndromic severe congenital neutropenia to classic G6PC3 deficiency (severe neutropenia along with cardiovascular and urogenital abnormalities) to severe G6PC3 deficiency (also known as Dursun syndrome, which includes features of classic G6PC3 deficiency along with severe lymphopenia, primary pulmonary hypertension, thymic hypoplasia, among other features). Kostmann disease or severe congenital neutropenia type 3 (SCN3) is due to recessive inheritance of pathogenic variants in HAX1 (which encodes HCLS1-associated protein X-1) and may result in seizures and developmental delay in addition to neutropenia. Along with neutropenia, variants in VPS45 inherited in an autosomal recessive manner (also known as severe congenital neutropenia type 5 [SNC5]) are associated with neutrophil dysfunction, bone marrow fibrosis, and nephromegaly due to renal extramedullary hematopoiesis. While loss-of-function variants in WAS, which is located on the X chromosome, cause Wiskott-Aldrich syndrome (characterized by thrombocytopenia, eczema, and recurrent infections), gain-of-function variants affecting the autoinhibitory structure of the protein, have been associated with congenital neutropenia, along with variable lymphopenia, decreased lymphocyte proliferation, and impaired phagocyte activity. Pathogenic variants in WIPF1 can present with similar findings to Wiskott-Aldrich syndrome. Severe neutropenia may also be present as part of a multisystem disorder. Barth syndrome, due to pathogenic variants in TAZ, which is located on the X-chromosome, is characterized by neutropenia, cardio- and skeletal myopathy, growth delay, and distinctive facial features. Biallelic variants in C16orf57 manifest as poikiloderma with neutropenia; the neutropenia may be cyclical. In Cohen syndrome, an autosomal recessive disorder due to variants in COH1 (also known as VPS13B), neutropenia is accompanied by hypotonia, developmental delays, microcephaly, failure to thrive in infancy, truncal obesity in adolescent years, ophthalmologic findings, joint hypermobility, a cheerful disposition, and characteristic facial features. Glycogen storage disease type I (GSDI), caused by biallelic pathogenic variants in either G6PC or SLC37A4, when untreated can result in chronic neutropenia and impaired neutrophil and monocyte function, as well as the characteristic findings that include accumulation of glycogen and fat in the liver and kidneys. Pathogenic variants in LAMTOR2/MAPBPIP have been shown to result in neutropenia, decreased cytotoxic activity of CD8+ T-cells, short stature, and hypopigmented skin. Persistent or intermittent neutropenia is often a presenting feature of Shwachman-Diamond syndrome (SDS), which is also characterized by exocrine pancreatic dysfunction (with malabsorption, malnutrition, and growth failure), bone abnormalities, and hematologic abnormalities (single- or multilineage cytopenias along with predisposition to myelodysplastic syndrome and acute myelogenous leukemia). SDS is an autosomal recessive disorder due to pathogenic variants in SBDS. Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome is characterized by neutropenia in addition to hypogammaglobulinemia, and susceptibility to human papillomavirus. It is due to autosomal dominant pathogenic variants in CXCR4. Although most forms of Hermansky-Pudlak syndrome do not include significant neutropenia, type 2 caused by variants in AP3B1 can be associated with persistent neutropenia and increased infections in addition to the typical findings of tyrosinase-positive oculocutaneous albinism, platelet storage pool deficiency, pulmonary fibrosis, and granulomatous colitis. Few patients with RAC2 pathogenic variants have been identified, but neutrophil dysfunction
appears to be a feature, though CD11b expression and specific granule release appear to be preserved. Both individuals with dominant and individuals with recessive inheritance have been identified, with and without additional associated phenotypic findings. GATA-binding protein (GATA2) deficiency demonstrates a wide spectrum of clinical presentations, including neutropenia. Most variants appear to arise de novo (spontaneously) and are then transmitted in an autosomal dominant manner. If the clinical phenotype strongly suggests GATA2 deficiency, this gene is available as a stand-alone test (see GATA2 / GATA-Binding Protein 2 (GATA2), Full Gene, Next-Generation Sequencing, Varies). This panel does not evaluate for somatic (acquired) ASXL1 mutations associated with GATA2 deficiency. Table 1.

Genes included in the Congenital Neutropenia/Neutrophil-Related PID Gene Panel | GENE SYMBOL | PROTEIN | OMIM | INCIDENCE | INHERITANCE | PHENOTYPE | DISORDER
--- | --- | --- | --- | --- | --- | --- | ---
AP3B1 | AP-3 complex subunit beta-1 isoform 1 | 603401 | Rare | AR | Hermansky-Pudlak syndrome 2 | CSF3R | Granulocyte colony-stimulating factor receptor isoform a precursor | 138971 | AR, acquired | Severe congenital neutropenia | CXCR4 | C-X-C chemokine receptor type 4 isoform b | 162643 | AD | Myelokathexis, isolated, WHIM syndrome (AD) | ELANE | Neutrophil elastase preproprotein | 130130 | 2:1,000,000-3:1,000,000 (SCN); 1:1,000,000 (cyclic neutropenia) | AD | Severe congenital neutropenia (SCN), cyclic neutropenia | G6PC3 | Glucose-6-phosphatase | 611045 | AR | Dursun syndrome, severe congenital neutropenia (SCN) | GATA2 | Endothelial transcription factor GATA-2 isoform 1 | 137295 | AD | Immunodeficiency 21, Emberger syndrome, susceptibility to acute myeloid leukemia and myelodysplastic syndrome | GFI1 | Zinc finger protein Gfi-1 | 600871 | AD | Severe congenital neutropenia (SCN) | 2(AD), nonimmune chronic idiopathic neutropenia of adults HAX1 HCLS1-associated protein X-1 isoform a | 605998 | AR | Severe congenital neutropenia (SCN) | 3 | LAMTOR2 (MAPBPIP) | Regulator complex protein LAMTOR2 isoform 1 | 610389 | AR | Immunodeficiency due to defect in MAPBP-interacting protein | RAC2 | ras-Related C3 botulinum toxin substrate 2 | 602049 | AD/AR | Neutrophil functional defects | SBDS | Ribosome maturation protein | 607444 | AR | Shwachman-Diamond syndrome, susceptibility to aplastic anemia SLC37A4 Ddipeptidyl peptidase 1 isoform a | 602671 | AR | Glycogen storage disease Ib and 1c TAZ Tafazzin isoform 1 | 300394 | XL | Barth syndrome | USB1 (C16ORF57) | U6 snRNA phosphodiesterase isoform 1 | 613276 | Rare | AR | Poikiloderma with neutropenia | TAZ | Tafazzin isoform 1 | 300394 | XL | Barth syndrome | WIPF1 | WAS/WASL-interacting protein family member 1 | 602357 | In progress | Wiskott-Aldrich syndrome 2 | AD | autosomal dominant AR=autosomal recessive XL=X-linked

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of congenital neutropenia, cyclic neutropenia, or other primary immunodeficiency disorder (PIDD) presenting with significant neutropenia Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with PIDD characterized by significant neutropenia allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

CONGR
82466

Congo Red Stain (Bill Only)

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

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

CTDC
83631

Connective Tissue Diseases Cascade, Serum

Clinical Information: The following diseases are often referred to as connective tissue diseases: rheumatoid arthritis (RA), lupus erythematosus (LE), scleroderma (systemic sclerosis) CREST syndrome (calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia), Sjogren syndrome, mixed connective tissue disease (MCTD), and polymyositis. Connective tissue diseases (systemic rheumatic diseases) are characterized by immune-mediated inflammation that involves the joints, skin, and visceral organs. These diseases are also accompanied by antibodies to a host of nuclear and cytoplasmic autoantigens. The diagnosis of a connective tissue disease is based on clinical signs and symptoms and characteristic radiographic, histopathologic, and serologic findings. Certain connective tissue diseases are characterized by autoantibodies that are highly specific for individual diseases (see table). Connective tissue diseases often present clinically with signs and symptoms that are nonspecific, including constitutional signs (eg, fever, weight loss, fatigue, and arthralgias). Accordingly, consideration of the possibility of a connective tissue disease is common on initial clinical presentation and testing for antibodies to autoantigens associated with connective tissue diseases is often performed early in the evaluation of many patients. (1) Autoantibodies with High Specificity for Individual Connective Tissue Diseases Cyclic citrullinated peptide antibodies RA dsDNA antibodies LE Scl 70 antibodies (topoisomerase 1) Scleroderma Jo 1 antibodies (histidyl tRNA synthetase) Polymyositis SSA/Ro and SSB/La antibodies Sjogren syndrome RNP antibodies (in isolation) MCTD Sm antibodies LE Ribosome P antibodies LE Centromere antibodies CREST syndrome In this test, serum is tested initially for the presence of antinuclear antibodies (ANA) and for cyclic citrullinated peptide (CCP) antibodies. The presence of CCP antibodies indicates a strong likelihood of RA. (2) The presence of ANA supports the possibility of a connective tissue disease, and the level of ANA is used to identify sera for second-order testing for antibodies to double-stranded DNA (dsDNA) and the other autoantigens. The decision threshold for performing the second-order tests is based on empirical data derived from testing patients with varying levels of ANA and was chosen to minimize testing when positive results for dsDNA and other antibodies are very unlikely. (3) The testing algorithm is useful in the initial evaluation of patients and performs best in clinical situations in which the prevalence of disease is low. (4)

Useful For: Evaluation of patients with signs and symptoms compatible with connective tissue diseases

Interpretation: Interpretive comments are provided. See individual unit codes for additional information.
Reference Values:
ANTINUCLEAR ANTIBODIES (ANA)
< or =1.0 U (negative)
1.1-2.9 U (weakly positive)
3.0-5.9 U (positive)
> or =6.0 U (strongly positive)
Reference values apply to all ages.

CYCLIC CITRULLINATED PEPTIDE ANTIBODIES, IgG
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-59.9 U (positive)
> or =60.0 U (strong positive)
Reference values apply to all ages.

testing for drugs by class. All positive immunoassay screening results are confirmed by gas chromatography-mass spectrometry (GC-MS) and quantitated, before a positive result is reported. This assay was designed to test for and confirm by GC-MS the following: -Barbiturates -Cocaine -Tetrahydrocannabinol The targeted opioid, benzodiazepine, and stimulant screen portions are performed by liquid chromatography-tandem mass spectrometry, high-resolution accurate mass (LC-MS/MS HRAM) and are completed for all opioids, benzodiazepines, and stimulants. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression depending on the dose. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay doesn’t hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone). Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures and are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent and metabolites in the urine. Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All of the other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration (DEA) scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

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

**Interpretation:** A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. See individual tests (eg, COKEU / Cocaine and Metabolite Confirmation, Random, Urine) for more information. For information about drug testing, including estimated detection times, see Specific Drug Groups at https://www.mayocliniclabs.com/test-info/drug-book/index.html

**Reference Values:**

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

**DRUG IMMUNOOASSAY PANEL:**
- Negative
- Screening cutoff concentrations:
  - Barbiturates: 200 ng/mL
  - Cocaine (benzoylecggonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

TARGETED OPIOID SCREEN:
Not Detected

Cutoff concentrations:
- Codeine: 25 ng/mL
- Codeine-6-beta-glucuronide: 100 ng/mL
- Morphine: 25 ng/mL
- Morphine-6-beta-glucuronide: 100 ng/mL
- 6-monoacetylmorphine: 25 ng/mL
- Hydrocodone: 25 ng/mL
- Norhydrocodone: 25 ng/mL
- Dihydrocodeine: 25 ng/mL
- Hydromorphone: 25 ng/mL
- Hydromorphone-3-beta-glucuronide: 100 ng/mL
- Oxycodone: 25 ng/mL
- Noroxycodone: 25 ng/mL
- Oxymorphone: 25 ng/mL
- Oxymorphone-3-beta-glucuronide: 100 ng/mL
- Noroxymorphone: 25 ng/mL
- Fentanyl: 2 ng/mL
- Norfentanyl: 2 ng/mL
- Meperidine: 25 ng/mL
- Normeperidine: 25 ng/mL
- Naloxone: 25 ng/mL
- Naloxone-3-beta-glucuronide: 100 ng/mL
- Methadone: 25 ng/mL
- EDDP: 25 ng/mL
- Propoxyphene: 25 ng/mL
- Norpropoxyphene: 25 ng/mL
- Tramadol: 25 ng/mL
- O-desmethyltramadol: 25 ng/mL
- Tapentadol: 25 ng/mL
- N-desmethyltapentadol: 50 ng/mL
- Tapentadol-beta-glucuronide: 100 ng/mL
- Buprenorphine: 5 ng/mL
- Norbuprenorphine: 5 ng/mL
- Norbuprenorphine glucuronide: 20 ng/mL

TARGETED BENZODIAZEPINE SCREEN:
Not Detected

Cutoff concentrations:
- Alprazolam: 10 ng/mL
- Alpha-Hydroxyalprazolam: 10 ng/mL
- Alpha-Hydroxyalprazolam Glucuronide: 50 ng/mL
- Chlordiazepoxide: 10 ng/mL
- Clobazam: 10 ng/mL
- N-Desmethylclobazam: 200 ng/mL
- Clonazepam: 10 ng/mL
- 7-aminoclonazepam: 10 ng/mL
- Diazepam: 10 ng/mL
- Nordiazepam: 10 ng/mL
- Flunitrazepam: 10 ng/mL
- 7-aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL  
2-Hydroxy Ethyl Flurazepam: 10 ng/mL  
Lorazepam: 10 ng/mL  
Lorazepam Glucuronide: 50 ng/mL  
Midazolam: 10 ng/mL  
Alpha-Hydroxy Midazolam: 10 ng/mL  
Oxazepam: 10 ng/mL  
Oxazepam Glucuronide: 50 ng/mL  
Prazepam: 10 ng/mL  
Temazepam: 10 ng/mL  
Temazepam Glucuronide: 50 ng/mL  
Triazolam: 10 ng/mL  
Alpha-Hydroxy Triazolam: 10 ng/mL  
Zolpidem: 10 ng/mL  
Zolpidem Phenyl-4-Carboxylic acid: 10 ng/mL

**TARGETED STIMULANT SCREEN:**
Not Detected

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

**Clinical References:**  

**Copeptin proAVP, Plasma**

**Clinical Information:** Arginine vasopressin (AVP) and copeptin (also known as copeptin proAVP or copeptin AVP) are derived from the same precursor peptide. Copeptin has been proposed as a more stable, potentially superior, surrogate marker of AVP in the assessment of water balance disorders. Unlike AVP, copeptin is stable in plasma. Both copeptin and AVP are responsive to osmotic stimuli and increase in response to water deprivation. In healthy subjects, water deprivation causes the plasma osmolality to rise above approximately 280-290 mOsmol/kg, leading to the release of AVP and copeptin into the plasma.
Copeptin increases gradually with fasting and water deprivation and declines rapidly after intake of water and/or food. Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmolar stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI). The determination of the underlying disease pathology in patients with polyuria and altered plasma osmolality is often difficult. Polyuria can be related to insufficient AVP (central DI), reduced sensitivity to AVP (nephrogenic DI), or excessive water intake. Measurement of plasma copeptin concentration has been shown to be useful in the investigation of these AVP-related disorders. Additionally, utilization of copeptin has been proposed in the assessment of syndrome of inappropriate antidiuretic (SIADH). Copeptin is also a marker of acute hemodynamic stress, and has been reported to aid in the prognosis or diagnosis of several cardiac disorders such as acute coronary syndrome, stable coronary artery disease, congestive heart failure, and acute ischemic stroke. Some studies have demonstrated that copeptin may improve prediction of mortality and heart disease outcome when combined with natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP).

**Useful For:** The investigation of the differential diagnosis of patients with water balance disorders, including diabetes insipidus, in conjunction with osmolality and hydration status may aid in the evaluation of cardiovascular disease in conjunction with other cardiac markers

**Interpretation:** While secreted in equimolar concentrations in conjunction with arginine vasopressin (AVP), measured plasma concentrations of copeptin do not correlate strongly with AVP concentrations due to in vivo and in vitro differences in stability. Copeptin is a more stable surrogate biomarker of AVP release. The clinical utility of copeptin of differentiating polyuria and water balance disorders has been demonstrated in a number of studies, when used in conjunction with osmolality and hydration status. In a prospective clinical study, an algorithm was established based on patients with polyuria-polydipsia syndrome (n=55). A nonwater deprived baseline copeptin concentration of 21.4 pmol/L or greater was found to be consistent with the presence of nephrogenic diabetes insipidus (DI). In a described algorithm(1), patients with a copeptin concentrations of under 21.4 pmol/L and a copeptin cut-off of 4.9 pmol/L after fluid deprivation, was used to distinguish between complete or partial DI (<4.9 pmol/L) and primary polydipsia (> or =4.9 pmol/L). Central DI may also be differentiated from nephrogenic DI by measuring copeptin during a stimulus for AVP release such as a water deprivation test. Copeptin concentrations obtained in the process of a water deprivation test can be difficult to interpret because of variation in water deprivation protocols. Patients with psychogenic polydipsia will either have a normal response to water deprivation or, in long-standing cases, show a pattern suggestive of mild nephrogenic DI. Expert consultation is recommended in these circumstances. Although the water-deprivation test is considered the reference standard for the evaluation of DI, measurement of saline stimulated copeptin was shown to be more accurate than the water-deprivation test.(2) In this indirect water deprivation test with a cutoff of 4.9 pmol/L or less indicated central DI while a concentration greater than 4.9 pmol/L indicated primary polydipsia. An elevated plasma copeptin AVP concentration in a hyponatremic patient may be indicative of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). However copeptin determination alone is not typically sufficient to distinguish SIADH from other hyponatremic disorders.(3) Elevations of plasma copeptin in patients with symptoms of heart failure may be prognostic of short and long term mortality. In patients with heart failure (HF) following a myocardial infarction (MI), elevations in copeptin are associated with severity of HF and poorer prognosis.(4) In a cohort of patients with class III or IV HF, copeptin concentrations of 40 pmol/L or greater significantly increased the risk of death or need for cardiac transplantation. The combination of elevated copeptin and hyponatremia was an even stronger predictor of heart failure, independent of B-type natriuretic peptide (BNP) and cardiac troponin (cTn) concentrations.(5)

**Reference Values:**
- Non-water deprived, non-fasting adults: <13.1 pmol/L
- Water deprived, fasting adults: <15.2 pmol/L
- Non-water deprived, non-fasting pediatric patients: <14.5 pmol/L

**Note:**
2. The reference interval for fasting and water deprived adults (at least 8 hours of fasting and water deprivation)
deprivation) was determined from an in-house Mayo study.


Copper, 24 Hour, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an adenosine triphosphate (ATP)-dependent transporter protein. Variants in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin or due to allelic variances in cellular metal ion transporters. Hypercupricuria (increased urinary copper) is also found in hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Low urine copper levels are seen in malnutrition, hypoproteinemias, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

Useful For: Investigation of Wilson disease and obstructive liver disease using a 24-hour urine specimen

Interpretation: Humans normally excrete less than 60 mcg/day of copper in the urine. Urinary copper excretion greater than 60 mcg/day may be seen in: -Wilson disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

Reference Values:
0-17 years: not established
CUT

Copper, Liver Tissue

Clinical Information: Homeostatic regulation of copper metabolism is very complex. The liver is the key organ to facilitate copper storage and incorporation of copper into the transport protein ceruloplasmin. Intestinal absorption and biliary excretion also play major roles in the regulation of copper homeostasis. Abnormal copper metabolism is associated with liver disease. Elevated serum copper concentrations are seen in portal cirrhosis, biliary tract disease, and hepatitis, probably because excess copper that would normally be excreted in the bile is retained in circulation. In primary biliary cirrhosis, ceruloplasmin is high, resulting in high serum copper. Lesser elevations of hepatic copper are found in chronic copper poisoning, obstructive jaundice, and certain cases of hepatic cirrhosis. Reduced serum copper concentration is typical of Wilson disease (hepatolenticular degeneration). Wilson disease is characterized by liver disease, neurologic abnormalities, and psychiatric disturbances. Kayser-Fleischer rings are normally present and urinary copper excretion is increased, while serum copper and ceruloplasmin are low.

Useful For: Diagnosing Wilson disease and primary biliary cirrhosis using liver tissue specimens

Interpretation: The constellation of symptoms associated with Wilson disease (WD), which includes Kayser-Fleischer rings, behavior changes, and liver disease, is commonly associated with liver copper concentration above 250 mcg/g dry weight. VERY HIGH >1000 mcg/g dry weight: This finding is strongly suggestive of Wilson disease. HIGH 250-1000 mcg/g dry weight: This finding is suggestive of possible Wilson disease. MODERATELY HIGH 50-250 mcg/g dry weight: Excessive copper at this level can be associated with cholestatic liver disease, such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and familial cholestatic syndrome. Heterozygous carriers for Wilson disease occasionally have modestly elevated values, but rarely higher than 125 mcg/g of dry weight. In general, the liver copper content is higher than 250 mcg/g dried tissue in patients with Wilson disease. If any of the above findings are without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Genetic testing for Wilson disease (WDZ / Wilson Disease, Full Gene Analysis, Varies) is available at Mayo Clinic Laboratories, call 800-533-1710 if you need additional assistance. In patients with elevated levels of copper without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered.

Reference Values:
<50 mcg/g dry weight

**Copper, Serum**

**Clinical Information:** Copper (Cu) is an important trace element that is associated with a number of metalloproteins. Cu in biological material is complexed with proteins, peptides, and other organic ligands. Up to 90% of Cu exported from the liver into peripheral blood is in the protein bound form either to ceruloplasmin, transcuprein, or metallothionein. A smaller amount of Cu in plasma (<10%) is bound to albumin by specific peptide sequences, and this Cu is in equilibrium with plasma amino acids. The ceruloplasmin molecule contains 6 to 8 atoms of Cu per molecule with 6 atoms of Cu involved in the protein's ferroxidase and free radical scavenging activities. The other 1 to 2 atoms of Cu are termed "labile" and may allow ceruloplasmin to act as a Cu transporter, with a pool of Cu being exchanged between albumin, transcuprein, and the labile sites of ceruloplasmin. Low serum copper, most often due to excess iron or zinc ingestion and infrequently due to dietary copper deficit, results in severe derangement in growth and impaired erythropoiesis. Low serum copper is also observed in hepatolenticular degeneration (Wilson disease) due to a decrease in the synthesis of ceruloplasmin and allelic variances in cellular metal ion transporters. In Wilson disease, the albumin-bound copper may actually be increased, but ceruloplasmin copper is low, resulting in low serum copper. However, during the acute phase of Wilson disease (fulminant hepatic failure), ceruloplasmin and copper may be normal; in this circumstance, hepatic inflammation causes increased release of ceruloplasmin. It is useful to relate the degree of liver inflammation to the ceruloplasmin and copper-see discussion on hypercupremia below. Significant hepatic inflammation with normal ceruloplasmin and copper suggest acute Wilson disease. Other disorders associated with decreased serum copper concentrations include malnutrition, hypoproteinemina, malabsorption, nephrotic syndrome, Menkes disease, copper toxicity, and megadosing of zinc-containing vitamins (zinc interferes with normal copper absorption from the gastrointestinal tract). Hypercupremia is found in primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, malignant diseases (including leukemia), thyrotoxicosis, and various infections. Serum copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Since the gastrointestinal (GI) tract effectively excludes excess copper, it is the GI tract that is most affected by copper ingestion. Increased serum concentration does not, by itself, indicate copper toxicity.

**Useful For:** Diagnosis of: -Wilson disease -Primary biliary cirrhosis -Primary sclerosing cholangitis

**Interpretation:** Serum copper below the normal range is associated with Wilson disease, as well as a variety of other clinical situations (see Clinical Information). Excess use of denture cream containing zinc can cause hypocupremia. Serum concentrations above the normal range are seen in primary biliary cirrhosis and primary sclerosing cholangitis, as well as a variety of other clinical situations (see Clinical Information).

**Reference Values:**

- 0-2 months: 0.40-1.40 mcg/mL
- 3-6 months: 0.40-1.60 mcg/mL
- 7-9 months: 0.40-1.70 mcg/mL
- 10-12 months: 0.80-1.70 mcg/mL
- 13 months-10 years: 0.80-1.80 mcg/mL
- > or =11 years: 0.75-1.45 mcg/mL

CUCRU

Copper/Creatinine Ratio, Random, Urine

**Clinical Information:** The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an adenosine triphosphate (ATP)-dependent transporter protein. Variants in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin or due to allelic variances in cellular metal ion transporters. Hypercupriuria (increased urinary copper) is also found in hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Low urine copper levels are seen in malnutrition, hypoproteinemia, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

**Useful For:** Investigation of Wilson disease and obstructive liver disease using a random urine specimen

**Interpretation:** Humans normally excrete less than 60 mcg/24 hour in the urine. Urinary copper excretion greater than 60 mcg/24 hour may be seen in: - Wilson disease - Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) - Nephrotic syndrome (due to leakage through the kidney) - Chelation therapy - Estrogen therapy - Mega dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

**Reference Values:**

- **Males:**
  - 0-17 years: not established
  - > or =18 years: 9-43 mcg/g creatinine

- **Females:**
  - 0-17 years: not established
  - > or =18 years: 7-72 mcg/g creatinine


CORI

Coriander, IgE, Serum

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**FCORG 57526 Corn IgG**

**Interpretation:**

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

**FCOR4 57569 Corn IgG4**

**Interpretation:**

**Reference Values:** Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of
food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

**Corn Pollen, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to corn pollen

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to corn-food. Defining the allergen responsible for
eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic
episode. - To confirm sensitization prior to beginning immunotherapy.

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

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<table>
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<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson, MR

CORTC 88221
Corticosterone, Serum

Clinical Information: Corticosterone is a steroid hormone and a precursor molecule for aldosterone. It
is produced from deoxycorticosterone, further converted to 18-hydroxy corticosterone and, finally, to
aldosterone in the mineralocorticoid pathway. The adrenal glands, ovaries, testes, and placenta produce
steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids, and
sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3
major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various
levels of each pathway, intermediate products can move into the respective adjacent pathways via
additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions).
Corticosterone is the first intermediate in the corticoid pathway with significant mineral corticoid activity.
Its synthesis from 11-deoxycorticosterone is catalyzed by 11 beta-hydroxylase 2 (CYP11B2) or by 11
beta-hydroxylase 1 (CYP11B1). Corticosterone is in turn converted to 18-hydroxy corticosterone and
finally to aldosterone, the most active mineral corticoid. Both of these reactions are catalyzed by
CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and
18-methyloxidase (also known as aldosterone synthase) activity. The major diagnostic utility of
measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in
particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency
with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1.
Concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or at least individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require corticoid levels are often substantially elevated in healthy newborns in the first few hours of life and to be exercised in interpreting the mineral corticoid results in infants younger than 7 days; mineral reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal upper limit of the normal reference range on a morning blood draw. Elevations in 11-deoxycortisol are elevated, usually to at least 2 to 3 times (more typically 20 to 300 times) the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, hirsutism, polycystic ovarian syndrome or infertility, as well as in possible premature adrenarche and pubarche in both genders. Measurement of the various precursors of mature mineral corticoid and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of corticosterone is used as an adjunct to 11-deoxycorticosterone and 11-deoxycortisol (also known as compound S) measurement in the diagnosis of: -CYP11B1 deficiency (associated with cortisol deficiency) -The less common CYP11B2 deficiency (no cortisol deficiency) -The rare glucocorticoid responsive hyperaldosteronism (where expression of the gene CYP11B2 is driven by the CYP11B1 promoter, thus making it responsive to adrenocorticotropic hormone: ACTH rather than renin) -Isolated loss of function of the 18-hydroxylase or 18-methylxidase activity of CYP11B2 For other forms of CAH, the following tests might be relevant: -21-Hydroxylase deficiency: Â - OHPG / 17-Hydroxyprogesterone, Serum Â - ANST / Androstenedione, Serum Â - 21DOC / 21-Deoxycortisol, Serum Â -3-Beta-steroid dehydrogenase deficiency: Â - 17PRN / Pregnenolone and 17-Hydroxypregnenolone -17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): Â - 17PRN / Pregnenolone and 17-Hydroxyprogrenolone Â - PGSN / Progesterone, Serum Â -OHPG / 17-Hydroxyprogesterone, Serum - DHEA_ / Dehydroepiandrosterone (DHEA), Serum - ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. When evaluating for suspected 11-hydroxylase deficiency, this test should be used in conjunction with measurements of 11-deoxycortisol, 11-corticosteone, 18-hydroxy cortisol, cortisol, renin, and aldosterone. When evaluating congenital adrenal hyperplasia newborn screen-positive children, this test should be used in conjunction with 11-deoxycortisol and 11-deoxycorticosterone measurements as an adjunct to 17-hydroxyprogesterone, aldosterone and cortisol measurements. Useful For: Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11 beta-hydroxylase 1 (CYP11B1) versus 11 beta-hydroxylase 2 (CYP11B2) deficiency, and the diagnosis of glucocorticoid-responsive hyperaldosteronism. Evaluating congenital adrenal hyperplasia newborn screen-positive children, when elevations of 17-hydroxyprogesterone are only moderate, thereby suggesting possible 11-hydroxylase deficiency Interpretation: In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 microgram/dL for a morning draw). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20 to 300 times) the upper limit of the normal reference range on a morning blood draw. Elevations in 11-deoxycortisol are usually relatively greater than those of 11-deoxycorticosterone because of the presence of intact 11 beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineral corticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineral corticoid results in infants younger than 7 days; mineral corticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require adrenocorticotropic hormone (ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone
will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2 gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from showing directly responsiveness of mineral corticoid production to ACTH1-24 injection. Normally, this has little, if any, effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineral corticoid levels fall after administration of dexamethasone. Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced, in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL (upper limit of reference range for newborns) to 2,000 or 3,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYP11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in these cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires 11-hydroxylation of 17-hydroxyprogesterone.

Reference Values:
< or =18 years: 18-1,970 ng/dL
>18 years: 53-1,560 ng/dL

Clinical References:

CORTO
65484
Cortisol, Free and Total, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism (Cushing disease) and hypocortisolism (Addison disease) can cause disease. Cortisol is also used to treat skin disease, allergic disorders, respiratory system disease, inflammatory disorders, and nephrotic syndrome. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is
Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralocorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11-beta-hydroxysteroid dehydrogenase isofrom-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein. Cortisol-binding globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to renal or liver disease may have a major impact on cortisol levels. Based on the study by Bancos(1), normal ranges of free cortisol found in patients without adrenal insufficiency were:

- Free cortisol at baseline: median 0.400 mcg/dL (interquartile range: IQR 2.5-97.5% - 0.110-1.425 mcg/dL)
- Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5-97.5% - 0.885-2.440 mcg/dL)
- Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5-97.5% - 1.230-2.930 mcg/dL)

Based on the study by Bancos,(1) the following cutoffs were calculated for exclusion of adrenal insufficiency:

- Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, area under the curve: AUC 0.81)
- Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99)
- Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1,190 ng/dL, AUC 0.99) (*please note that baseline free cortisol should not be used to exclude adrenal insufficiency given low performance)

The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy. Cortisol pediatric reference ranges are generally the same as adults as confirmed by peer-reviewed literature.
insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is less than 10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured and the short cosyntropin stimulation test performed. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

**Reference Values:**
FREE CORTISOL
6-10:30 a.m. Collection: 0.121-1.065 mcg/dL

TOTAL CORTISOL
5-25 mcg/dL (a.m.)
2-14 mcg/dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.


**Clinical References:**
due to excessive licorice consumption. Test may not be useful in the evaluation of adrenal insufficiency

**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. However, many normal individuals may also exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol measurements cannot be relied upon for the diagnosis of hypocorticalism.

**Reference Values:**
- 0-2 years: not established
- 3-8 years: 1.4-20 mcg/24 hours
- 9-12 years: 2.6-37 mcg/24 hours
- 13-17 years: 4.0-56 mcg/24 hours
- > or =18 years: 3.5-45 mcg/24 hours

Use the factor below to convert from mcg/24 hours to nmol/24 hours:

Conversion factor
Cortisol: mcg/24 hours x 2.76=nmol/24 hours (molecular weight=362.5)

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

**Clinical References:**
**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. The optimal specimen type for evaluation of primary adrenal insufficiency and hypopituitarism is serum (CORT / Cortisol, Serum).

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Males</th>
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<tbody>
<tr>
<td>0-2 years</td>
<td>3.0-120 mcg/g creatinine</td>
</tr>
<tr>
<td>3-8 years</td>
<td>2.2-89 mcg/g creatinine</td>
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<tr>
<td>9-12 years</td>
<td>1.4-56 mcg/g creatinine</td>
</tr>
<tr>
<td>13-17 years</td>
<td>1.0-42 mcg/g creatinine</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>1.0-119 mcg/g creatinine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>3.0-120 mcg/g creatinine</td>
</tr>
<tr>
<td>3-8 years</td>
<td>2.2-89 mcg/g creatinine</td>
</tr>
<tr>
<td>9-12 years</td>
<td>1.4-56 mcg/g creatinine</td>
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<tr>
<td>13-17 years</td>
<td>1.0-42 mcg/g creatinine</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>0.7-85 mcg/g creatinine</td>
</tr>
</tbody>
</table>

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine.

**Conversion factor**

- Cortisol: mcg/g creatinine x 312 = nmol/mol creatinine
- Cortisol molecular weight = 362.5
- Creatinine molecular weight = 113.12

**Clinical References:**

using a ratio known as the free cortisol index. This measurement takes into account the amount of total cortisol and CBG to give a percentage and ultimately absolute value of free cortisol. These methods do not take into account the possible variations in albumin levels. These calculations also rely on CBG, which can be lowered in critically ill patients despite normal adrenal function. Equilibrium dialysis best serves to separate free from bound cortisol without disrupting the bound fraction.

**Useful For:** Assessment of cortisol status in cases where there is known or a suspected abnormality in cortisol-binding proteins or albumin Assessment of adrenal function in the critically ill or stressed patient, thus preventing unnecessary use of glucocorticoid therapy

**Interpretation:** Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralocorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11-beta-hydroxysteroid dehydrogenase isoform-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein. Cortisol binding globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to renal or liver disease may have a major impact on free cortisol. Based on the study by Bancos,(1) normal ranges of free cortisol found in patients without adrenal insufficiency were: -Free cortisol at baseline: median 0.400 mcg/dL (interquartile range: IQR 2.5-97.5% - 0.110-1.425 mcg/dL) -Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5-97.5% - 0.885-2.440 mcg/dL) -Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5-97.5% - 1.230-2.930 mcg/dL) Based on the study by Bancos,(1) the following cutoffs were calculated for exclusion of adrenal insufficiency: -Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, area under the curve: AUC 0.81) -Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99) -Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1190 ng/dL, AUC 0.99) *baseline free cortisol should not be used to exclude adrenal insufficiency given low performance The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy.

**Reference Values:**

6-10:30 a.m. Collection: 0.121-1.065 mcg/dL


**CIVC 6347**  
Cortisol, Inferior Vena Cava, Serum  
**Reference Values:**  
No established reference values

**CLAV 6346**  
Cortisol, Left Adrenal Vein, Serum  
**Reference Values:**  
No established reference values

**CINP 9369**  
Cortisol, Mass Spectrometry, Serum  
**Reference Values:**  
No established reference values
**Clinical Information:** Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency See Steroid Pathways in Special Instructions.

**Useful For:** Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum. An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome This test is not recommended for evaluating response to metyrapone; DOC / 11-Deoxycortisol, Serum is more reliable.

**Interpretation:** In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased, and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured, and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

**Reference Values:**
5-25 mcg/dL (a.m.)
2-14 mcg/dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.


**Clinical References:** 1. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC: Urinary free cortisol and cortisone determined by high-performance liquid chromatography in the diagnosis of Cushing's
Cortisol, Right Adrenal Vein, Serum

Reference Values:
No established reference values

Cortisol, Saliva

Clinical Information: Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). Cushing syndrome results from overproduction of glucocorticoids because of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (elevated in the morning) and nadirs (low in the evening) for plasma ACTH and cortisol levels. The diurnal variation is lost in patients with Cushing syndrome and these patients have elevated levels of evening plasma cortisol. The measurement of late-night salivary cortisol is an effective and convenient screening test for Cushing syndrome.(1) In a recent study from the National Institute of Health, nighttime salivary cortisol measurement was superior to plasma and urine free cortisol assessments in detecting patients with mild Cushing syndrome.(2) The sensitivity of nighttime salivary cortisol measurements remained superior to all other measures. The distinction between Cushing syndrome and pseudo-Cushing states is most difficult in the setting of mild-to-moderate hypercortisolism. Subtle increases in salivary cortisol collected at midnight (cortisol of nadir) appear to be one of the earliest abnormalities in Cushing syndrome.

Useful For: Screening for Cushing syndrome Diagnosis of Cushing syndrome in patients presenting with symptoms or signs suggestive of the disease

Interpretation: Cushing syndrome is characterized by increased salivary cortisol levels, and late-night saliva cortisol measurements may be the optimum test for the diagnosis of Cushing syndrome. It is standard practice to confirm elevated results at least once. This can be done by repeat late-night salivary cortisol measurements, midnight blood sampling for cortisol (CORT / Cortisol, Serum), 24-hour urinary free cortisol collection (CORTU / Cortisol, Free, 24 Hour, Urine), or overnight dexamethasone suppression testing. Upon confirmation of the diagnosis, the cause of hypercortisolism, adrenal versus pituitary versus ectopic adrenocorticotropic hormone production, needs to be established. This is typically a complex undertaking, requiring dynamic testing of the pituitary adrenal axis and imaging procedures. Referral to specialized centers or in-depth consultation with experts is strongly recommended.

Reference Values:
7 a.m.-9 a.m.: 100-750 ng/dL
3 p.m.-5 p.m.: <401 ng/dL
11 p.m.-midnight: <100 ng/dL

Cortisol, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-90% of the plasma corticoids) plays a central role in glucose metabolism and in the body's response to stress. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary gland in response to corticotropin-releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6 a.m.-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to cortisol-binding globulin (CBG-transcortin) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). The free cortisol is the physiologically active form and is filterable by the renal glomerulus. Although hypercortisolism is uncommon, the signs and symptoms are common (eg, obesity, high blood pressure, increased blood glucose concentration). The most common cause of increased plasma cortisol levels in women is a high circulating concentration of estrogen (eg, estrogen therapy, pregnancy) resulting in increased concentration of cortisol-binding globulin. Spontaneous Cushing syndrome results from overproduction of glucocorticoids as a result of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Causes of hypocortisolism are: Addison disease-primary adrenal insufficiency Secondary adrenal insufficiency --Pituitary insufficiency --Hypothalamic insufficiency --Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

Useful For: Discrimination between primary and secondary adrenal insufficiency Differential diagnosis of Cushing syndrome This test is not recommended for evaluating response to metyrapone.

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased, and cortisol levels are decreased; in secondary adrenal insufficiency, both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is less than 10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. First, the basal plasma ACTH concentration should be measured, followed by the short cosyntropin stimulation test. For the cosyntropin (ACTH)-stimulation test, serum cortisol is measured before and at various time intervals after an ACTH injection. The criteria for a normal response are: An increase in serum cortisol to a peak value of at least 15 mcg/dL post-cosyntropin-Usually also associated with an increase in serum cortisol of at least 7 mcg/dL above the baseline (if baseline cortisol is >15 mcg/dL, this criterion does not apply)-Basal serum cortisol greater than 5 mcg/dL (criterion applies when blood drawn before 9 a.m.) False normal responses may be present in patients on oral estrogen therapy or in patients with mild secondary adrenal insufficiency. Other frequently used tests are the metyrapone and insulin-induced hypoglycemia test. Consult the Endocrine Testing Center at 800-533-1710 for testing information and interpretation of test results. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine, which utilizes liquid chromatography/tandem mass spectrometry (LC-MS/MS). A normal result makes the diagnosis unlikely. When cortisol measurement by immunoassay gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids, consider testing by LC-MS/MS; see CINP / Cortisol, Mass Spectrometry, Serum. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum.

Reference Values:
a.m.: 7-25 mcg/dL
p.m.: 2-14 mcg/dL

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

Corticosterone, Free, 24 Hour, Urine

**Clinical Information:** Corticosterone is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Corticosterone plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body’s response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating corticosterone is biologically active (free), with the majority of corticosterone inactive (protein bound). As plasma corticosterone values increase, free corticosterone (i.e., unconjugated corticosterone) increases and is filtered through the glomerulus. Urinary free corticosterone (UFC) correlates well with the concentration of plasma free corticosterone. UFC represents excretion of the circulating, biologically active, free corticosterone that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based corticosterone results. Corticosterone, a downstream metabolite of corticosterone, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxysteroid dehydrogenase (11-beta HSD), the enzyme that converts corticosterone to corticosterone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because corticosterone (but not corticosterone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

**Useful For:** Screening test for Cushing syndrome (hypercortisolism) Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (corticosterone to corticosterone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency.

**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of corticosterone and/or corticosterone. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed corticosterone and corticosterone. In these circumstances a synthetic glucocorticoid screen might be ordered (call 800-533-1710). Suppressed corticosterone and corticosterone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Further, many normal individuals also may exhibit a very low 24-hour urinary corticosterone excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary corticosterone measurements cannot be relied upon for the diagnosis of hypocorticalism. Patients with 11-beta HSD deficiency may have corticosterone to corticosterone ratios <1, whereas a ratio of 2:1 to 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to <1.

**Reference Values:**
- CORTISOL
  - 0-2 years: not established
  - 3-8 years: 1.4-20 mcg/24 hours
  - 9-12 years: 2.6-37 mcg/24 hours
CORTISONE
0-2 years: not established
3-8 years: 5.5-41 mcg/24 hours
9-12 years: 9.9-73 mcg/24 hours
13-17 years: 15-108 mcg/24 hours
> or =18 years: 17-129 mcg/24 hours

Use the factors below to convert each analyte from mcg/24 hours to nmol/24 hours:

Conversion factors
Cortisol: mcg/24 hours x 2.76=nmol/24 hours (molecular weight=362.5)
Cortisone: mcg/24 hours x 2.78=nmol/24 hours (molecular weight=360)

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


Cortisol/Cortisone, Free, Random, Urine
Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. It plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body’s response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

Useful For: Investigating suspected Cushing syndrome (hypercortisolism), when a 24-hour collection is prohibitive (ie, pediatric patients). Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption

Interpretation: Most patients with Cushing syndrome have increased urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm
the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol and cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Patients with 11-beta HSD deficiency may have cortisone to cortisol ratios less than 1, whereas a ratio of 2 or 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to less than 1.

Reference Values:
CORTISOL
Males
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 1.0-119 mcg/g creatinine
Females
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 0.7-85 mcg/g creatinine

CORTISONE
0-2 years: 25-477 mcg/g creatinine
3-8 years: 11-211 mcg/g creatinine
9-12 years: 5.8-109 mcg/g creatinine
13-17 years: 5.4-102 mcg/g creatinine
18-29 years: 5.7-153 mcg/g creatinine
30-39 years: 6.6-176 mcg/g creatinine
40-49 years: 7.6-203 mcg/g creatinine
50-59 years: 8.8-234 mcg/g creatinine
60-69 years: 10-270 mcg/g creatinine
> or =70 years: 12-311 mcg/g creatinine

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine:

Conversion factors
Cortisol: mcg/g creatinine x 312=nmol/mol creatinine
Cortisone: mcg/g creatinine x 314=nmol/mol creatinine

Cortisol molecular weight=362.5
Cortisone molecular weight=360.4
Creatinine molecular weight=113.12

Clinical Information: Corynebacterium diphtheriae is the etiological agent of diphtheria and occurs in 2 forms, respiratory and cutaneous diphtheria. Respiratory diphtheria may be further classified into pharyngeal, tonsillar, laryngeal, and the less common anterior nasal diphtheria. Due to vaccination programs in the United States, diphtheria is now a rarely reported disease. Corynebacterium diphtheriae is primarily spread by droplets from coughing or sneezing. The incubation period averages 2 to 5 days. The illness is characterized by fever, malaise, and sore throat with a distinguishing thick pseudomembrane present over the involved mucosa. A swab from beneath the pseudomembrane is the preferred specimen for culture. The organisms multiplying at the infection site produce a toxin, diphtheria toxin, which may result in systemic complications affecting the heart, nervous system, etc. In patients with a clinical diagnosis of possible diphtheria, appropriate specimens should be collected for culture; patients should be placed in appropriate isolation and consideration given to administration of empiric antitoxin (available in the United States through the Centers for Disease Control and Prevention) and antibiotics; respiratory and airway support may be required.

Useful For: Confirmation of the clinical diagnosis of diphtheria

Interpretation: A positive result supports a diagnosis of diphtheria. The pathogenesis of the associated disease relates to production phage-encoded diphtheria toxin. Since isolates of Corynebacterium diphtheriae may or may not harbor genes to produce the toxin, they should be further tested for diphtheria toxin production. When isolated, other potentially toxin-producing organisms (eg, Corynebacterium ulcerans, Corynebacterium pseudotuberculosis) will also be reported. A negative result is evidence against a diagnosis of diphtheria but does not definitively rule out this disease since culture may be negative because of prior antimicrobial therapy or organism present below the limit of detection of the assay.

Reference Values:
No growth of Corynebacterium diphtheriae


Cotton Fiber, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to cotton fiber

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

Reference Values:
Class IgE kU/L Interpretation

Cottonseed, IgE, Serum

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

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

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

Reference Values:

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 50.0-99.9</td>
<td>Strongly positive</td>
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</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Cottonwood, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to cottonwood Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

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

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<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Cow Epithelium, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to cow epithelium

<table>
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<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>


**COX-2 Immunostain, Technical Component Only**

**Clinical Information:** Cyclooxygenase 2 (COX-2) is an inducible enzyme involved in production of prostaglandins in inflammatory processes. It is involved in the response of cells to growth factors, tumor promoters, and cytokines that induce its expression. There is increased evidence that expression of COX-2 plays a role in development and progression of malignant epithelial tumors. Eighty five to 90% of colon cancers show over-expression of COX-2. COX-2 positivity has been correlated with a poor response to treatment and shorter overall survival.

**Useful For:** Identifying normal and neoplastic cells expressing cyclooxygenase-2 (COX-2)

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Coxiella burnetii (Q fever), Molecular Detection, PCR, Blood

Clinical Information: Coxiella burnetii, the causative agent of Q fever, is a small obligate intracellular bacterium that is distributed ubiquitously in the environment. The agent is acquired through aerosol exposure and generally causes mild respiratory disease. A small number of acute cases will advance to a chronic condition, which typically manifests as endocarditis. If left untreated, cases of Q fever endocarditis are fatal. Current diagnostic methods of Q fever endocarditis include serologic studies and histopathologic examination of excised cardiac tissue. These current methods are subjective and nonspecific, limiting usefulness in patient diagnostics. Evaluation of infected tissue, blood, or serum using PCR has been shown to be an effective tool for diagnosing C burnetii infection. Mayo Clinic Laboratories has developed a real-time PCR test that permits rapid identification of C burnetii. The assay targets a unique sequence of the shikimate dehydrogenase gene (aroE) present in C burnetii.

Useful For: Aiding in the diagnosis of Coxiella burnetii infection (eg, Q fever)

Interpretation: A positive result indicates the presence of Coxiella burnetii DNA. A negative result indicates the absence of detectable C burnetii DNA, but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of C burnetii DNA in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

Coxiella burnetii (Q fever), Molecular Detection, PCR, Varies

**Clinical Information:** Coxiella burnetii, the causative agent of Q fever, is a small obligate intracellular bacterium, which is associated with animals. It is acquired through aerosol exposure and generally causes mild respiratory disease. A small number of acute cases advance to a chronic infection, which typically manifests as endocarditis. Left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic studies may be nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using PCR may be a useful tool for diagnosing some cases of C burnetii infection. Mayo Clinic Laboratories has developed a real-time PCR test that rapidly detects C burnetii DNA in clinical specimens by targeting a sequence of the shikimate dehydrogenase gene (aroE) unique to C burnetii.

**Useful For:** Aiding in the diagnosis of Coxiella burnetii infection (eg, Q fever) using tissue specimens

**Interpretation:** A positive result indicates the presence of Coxiella burnetii DNA. A negative result indicates the absence of detectable C burnetii DNA, but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of C burnetii DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**CPOXZ 35395**

**CPOX Gene, Full Gene Analysis, Varies**

**Clinical Information:** Hereditary coproporphyria (HCP) is an autosomal dominant (AD) acute hepatic porphyria that presents with clinical attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HCP is also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. HCP is caused by AD mutations in the CPOX gene. Mutations may have incomplete penetrance. Homozygous mutations in CPOX have been reported in association with a more severe, phenotypically distinct condition called harderoporphyria that is characterized by neonatal hemolytic anemia with mild residual anemia during childhood and adulthood. Affected patients may also present with skin lesions and fecal harderporphyrin accumulation may be observed. This condition is inherited in an autosomal recessive pattern and all patients identified to date have been heterozygous or homozygous for the K404E mutation. For HCP, acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in distinguishing HCP from other forms of acute porphyria.

**Useful For:** Confirmation of hereditary coproporphyria (HCP) for patients with clinical features. This test should be ordered only for individuals with symptoms suggestive of HCP. Asymptomatic patients with a family history of HCP should not be tested until a mutation has been identified in an affected family member.

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

**Reference Values:**
An interpretive report will be provided.


**FCRAB 57674**

**Crab IgG**

**Interpretation:**

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

**CRAB 82745**

**Crab, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to crab Defining the allergen responsible for
eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or
anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**CRANB 86307**

**Cranberry, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing the diagnosis of an allergy to cranberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

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

**Reference Values:**

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</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Crayfish, IgE, Serum**

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

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

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

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</tr>
</tbody>
</table>

Reference values apply to all ages.


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Creatine Disorders Panel, Random, Urine

Clinical Information: Disorders of creatine synthesis, deficiency of arginine:glycine amidotransferases (AGAT), and guanidinoacetate methyltransferase (GAMT), and creatine transporter (SLC6A8) deficiency, are collectively described as creatine deficiency syndromes (CDS). AGAT and GAMT deficiencies are inherited in an autosomal recessive manner, while the creatine transporter defect is X-linked. All 3 disorders result in a depletion of cerebral creatine and typically present with global developmental delays, intellectual disability, and severe speech delay. Commonly, patients with CDS develop seizures. Patients with GAMT and the creatine transporter deficiency exhibit behavioral problems and features of autism. Female carriers for the creatine transporter deficiency can have intellectual disability and behavioral problems, and some develop seizures. Diagnosis is possible by measuring guanidinoacetate (GAA), creatine (Cr), and creatinine (Crn) in plasma and urine. The profiles are specific for each clinical entity. Patients with GAMT deficiency typically exhibit normal to low Cr, very elevated GAA, and low Crn. Patients with AGAT deficiency typically exhibit normal to low Cr, low GAA, and normal to low Crn. In comparison, elevated Cr, normal GAA, normal to low Crn, and an elevated Cr:Crn ratio characterize patients with creatine transporter defect. Treatment with oral supplementation of creatine monohydrate is available and effective for the AGAT and GAMT deficiencies. Early treatment has been reported to prevent disease manifestations in affected but presymptomatic newborn siblings of individuals with GAMT or AGAT deficiencies. Creatine supplementation has not been shown to improve outcomes in males with the creatine transporter defect. Female carriers of creatine transporter deficiency who have symptoms, however, have been reported to benefit from creatine supplementation.

Useful For: Evaluation of patients with a clinical suspicion of inborn errors of creatine metabolism including arginine:glycine amidotransferase deficiency, guanidinoacetate methyltransferase deficiency, and creatine transporter (SLC6A8) defect

Interpretation: Reports include concentrations of guanidinoacetate, creatine, and creatinine, and a calculated creatine:creatinine ratio. When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

Reference Values:
<table>
<thead>
<tr>
<th>Age</th>
<th>Creatinine (nmol/mL)</th>
<th>Guanidinoacetate (nmol/mL)</th>
<th>Creatine (nmol/mL)</th>
<th>Creatine/Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =31 days</td>
<td>430-5,240</td>
<td>9-210</td>
<td>12-2,930</td>
<td>0.02-0.93</td>
</tr>
<tr>
<td>32 days-23 months</td>
<td>313-9,040</td>
<td>16-860</td>
<td>18-10,490</td>
<td>0.02-2.49</td>
</tr>
<tr>
<td>2-4 years</td>
<td>1,140-12,820</td>
<td>90-1,260</td>
<td>200-9,210</td>
<td>0.04-1.75</td>
</tr>
<tr>
<td>5-18 years</td>
<td>1,190-25,270</td>
<td>40-1,190</td>
<td>60-9,530</td>
<td>0.01-0.96</td>
</tr>
<tr>
<td>&gt;18 years (male)</td>
<td>3,854-23,340</td>
<td>30-710</td>
<td>7-470</td>
<td>0.00-0.04 Females</td>
</tr>
<tr>
<td>Age</td>
<td>Creatinine (nmol/mL)</td>
<td>Guanidinoacetate (nmol/mL)</td>
<td>Creatine (nmol/mL)</td>
<td>Creatine/Creatinine</td>
</tr>
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<td>40-1,190</td>
<td>60-9,530</td>
<td>0.01-0.96</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>1,540-18,050</td>
<td>30-760</td>
<td>5-2810</td>
<td>0.00-0.46</td>
</tr>
</tbody>
</table>

**Clinical References:**

**Creatine Kinase (CK), Serum**

**Clinical Information:** Creatine kinase (CK) is an enzyme that catalyzes the reversible phosphorylation of creatine (Cr) by adenosine triphosphate (ATP). Physiologically, when muscle contracts, ATP is converted to adenosine diphosphate (ADP), and CK catalyzes the repophosphorylation of ADP to ATP using creatine phosphate as the phosphorylation reservoir. The CK enzyme is a dimer composed of subunits derived from either muscle (M) or brain (B). Three isoenzymes have been identified: striated muscle (MM), heart tissue (MB), and brain (BB). Normal serum CK is predominantly the CK-MM isoenzyme. CK activity is greatest in striated muscle (MM isoenzyme), heart tissue (MB isoenzyme), and brain (BB isoenzyme). Serum CK concentrations are reflective of muscle mass causing males to have higher concentrations than females. CK may be measured to evaluate myopathy and to monitor patients with rhabdomyolysis for acute kidney injury.

**Useful For:** Diagnosing and monitoring myopathies or other trauma, toxin, or drug-induced muscle injury

**Interpretation:** Serum creatine kinase (CK) activity may increase in patients with acute cerebrovascular disease or neurosurgical intervention and with cerebral ischemia as well as in nearly all patients when injury, inflammation, or necrosis of skeletal or heart muscle occurs, including:
- All types of muscular dystrophy particularly in progressive muscular dystrophy (particularly Duchenne sex-linked muscular dystrophy).
- Viral myositis, polymyositis, and similar muscle diseases
- Malignant hyperthermia, an inherited life-threatening condition characterized by high fever and brought on by administration of inhalation anesthesia
- Muscle trauma, which causes CK elevations within 12 hours of onset, peaking within 1 to 3 days, and declining 3 to 5 days after cessation of muscle injury
- Serum CK activities exceeding 200 times the upper reference limit may be found in acute rhabdomyolysis, putting the patient at great risk for developing acute renal failure.
- When given at pharmacologic doses, some drugs including statins, fibrates, antiretrovirals, and angiotensin II receptor antagonists
- Endocrine myopathy, for which hypothyroidism is a common cause, about 60% of hypothyroid subjects show an average
elevation of CK activity 5-fold greater than the upper reference limit - Normal childbirth causes a 6-fold elevation in maternal serum. For detection of myocardial infarction, changes in serum CK and its heart tissue (MB) isoenzyme have been largely replaced by the more cardiac-specific nonenzymatic markers, cardiac troponin I or T.

Reference Values:
Males
< or =3 months: not established
>3 months: 39-308 U/L
Females
< or =3 months: not established
>3 months: 26-192 U/L
Reference values have not been established for patients that are less than 3 months of age.
Note: Strenuous exercise or intramuscular injections may cause transient elevation of creatine kinase (CK).


Creatine Kinase Isoenzyme Reflex, Serum

Clinical Information: Creatine kinase (CK) activity is found in the cytoplasm of several human tissues; major sources of CK include skeletal muscle, myocardium, and the brain. Cytoplasmic CK isoenzymes are dimers of the subunits M and B (MM, MB, or BB). Brain tissue contains predominantly CK-BB (CK1). Skeletal muscle contains almost exclusively CK-MM (CK3). The myocardium contains approximately 30% of CK-MB (CK2), which has been called the "heart-specific" isoenzyme. CK-MB is increased in acute myocardial infarction (AMI); however, CK-MB has been replaced by troponin as the preferred biomarker for the diagnosis of AMI. Mitochondrial CK, located at the outer surface of the inner mitochondrial membrane, has been suggested to catalyze the rate-limiting step of energy transfer from mitochondrial adenosine triphosphate (ATP) with the formation of creatine phosphatase (CP). The CP molecule, which is smaller in size than ATP, diffuses to target organelles in the cytoplasm where its energy is transferred to ATP by cytoplasmic CK. CK activity results in nonaerobic production of ATP in muscle tissues during work. Macro CK refers to at least 2 forms of CK. Macro CK type I is an antibody-bound form of cytoplasmic CK. It migrates between CK-MM and CK-MB. Macro CK type II (mitochondrial CK) migrates slightly cathodic of CK-MM. Detection of macro forms of CK is the primary reason for electrophoresis of CK activity.

Useful For: Detecting the macro forms of creatine kinase (CK) Identifying the source of a CK elevation

Interpretation: Creatine kinase (CK)-MB appears in serum 4 to 6 hours after the onset of pain in a myocardial infarction, peaks at 18 to 24 hours, and may persist for 72 hours. CK-MB may also be elevated in cases of carbon monoxide poisoning, pulmonary embolism, hypothyroidism, crush injuries, and muscular dystrophy. Extreme elevations of CK-MB can be associated with skeletal muscle cell turnover as in polymyositis, and to a lesser degree in rhabdomyolysis, as seen in strenuous exercise, particularly in the conditioned athlete. CK-BB can be elevated in patients with head injury, in neonates, and in some cancers such as prostate cancer and small cell carcinoma of the lung. It can also be elevated in other malignancies; however, the clinical usefulness of CK-BB as a tumor marker needs further investigation. The presence of macro CK can explain an elevation of total CK. It does not rise and fall as rapidly as CK-MM and CK-MB in muscle injury. Macro CK type II (mitochondrial CK) is rarely observed. It is only seen in acutely ill patients with malignancies and other severe illnesses with a high-associated mortality, such as liver disease and hypoxic injury.

Reference Values:
CREATINE KINASE, TOTAL
Males
< or =3 months: not established
>3 months: 39-308 U/L
Females
< or =3 months: not established
>3 months: 26-192 U/L
Reference values have not been established for patients that are less than 3 months of age.
Note: Strenuous exercise or intramuscular injections may cause transient elevation of creatine kinase (CK).

CREATINE KINASE ISOENZYMES
MM: 100%
MB: 0%
BB: 0%

Clinical References:

Creatinine Clearance, Serum and 24 Hour Urine

Clinical Information: Estimated GFR Using Serum Creatinine Alone: Estimated glomerular filtration rate (eGFR) is calculated using the 2009 CKD Epidemiology Collaboration (CKD-EPI) equation: eGFR(CKD-EPI) =141 x min(Scr/k, 1)alpha x max(Scr/k,1)-1.209 x 0.993 age x 1.018 (if patient is female) x 1.159 (if patient is black) -where age is in years -k is 0.7 for females and 0.9 for males -alpha is -0.329 for females and -0.411 for males -min indicates the minimum of Scr/k or 1 -max indicates the maximum of Scr/k or 1 Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with chronic kidney disease (CKD) and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Reasons given for routine reporting of eGFR with every serum creatinine in adult (18 and over) patients include:
-GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age, sex, and, to a lesser extent, race, on creatinine production further cloud interpretation. -Serum creatinine is commonly measured in routine clinical practice. Albuminuria (>30 mg/24 hour or urine albumin to creatinine ratio >30 mg/g) may be a more sensitive marker of early renal disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. -Monitoring of kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. -The CKD-EPI equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m[2]) using sex, age, and race. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The CKD-EPI equation does require race (African American or non-African American), which also may not be readily available. For this reason, eGFR values for both African Americans and non-African Americans are reported. The difference between the 2 estimates is typically about 20%. The patient or provider can decide which result is appropriate for a given patient.
The Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group clinical practice guidelines,(1) as further defined by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary,(2) provide the following recommendations for reporting and interpretation of serum creatinine and eGFR: 1.4.3: Evaluation of GFR -1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. -1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (2B) -1.4.3.3: We recommend that
clinicians: --Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone.--Understand clinical settings in which eGFR creat is less accurate. -1.4.3.4: We recommend that clinical laboratories should: --Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.--Report eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat. --Report eGFRcreat in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation. When reporting serum creatinine: -We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (mmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL). When reporting eGFRcreat: -We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m(2) in adults using the units mL/min/1.73 m(2). -We recommend eGFRcreat levels less than 60 mL/min/1.73 m(2) should be reported as "decreased". 1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions Creatinine Clearance: Creatinine is derived from the metabolism of creatine from skeletal muscle and dietary meat intake, and is released into the circulation at a relatively constant rate. Thus, the serum creatinine concentration is usually stable. Creatinine is freely filtered by glomeruli and not reabsorbed or metabolized by renal tubules. Therefore, creatinine clearance can be used to assess GFR. However, approximately 15% of excreted urine creatinine is derived from proximal tubular secretion. Because of the tubular secretion of creatinine, creatinine clearance typically overestimates true GFR by 10% to 15%. Creatinine clearance is usually determined from measurement of creatinine in a 24-hour urine specimen and from a serum specimen obtained during the same collection period. However, shorter time periods can be used. A key consideration is accurate timing and collection of the urine sample. Creatinine clearance normalized to body surface area is calculated by the equation: 2.54 cm=1 inch 1 kg=2.2 pounds (lbs) Patient surface area (SA)=wt (kg)(0.425) X ht (cm)(0.725) X 0.007184 Urine conc (mg/dL) x 24 hr urine volume (mL) Uncorr creat clear= 1440 minutes mL/min Serum creat (mg/dL) Urine conc (mg/dL) x 24 hr urine volume (mL) X 1.73 m(2) Patient SA Corr creat clear= 1440 minutes mL/min/1.73m(2) Serum creat (mg/dL)

Useful For: Estimation of glomerular filtration rate

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate (GFR). This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible, including drug effects or decreases in effective renal perfusion (eg, volume depletion, heart failure). Increased creatinine clearance is often referred to as hyperfiltration and is most commonly seen during pregnancy or in patients with early diabetes mellitus, before diabetic nephropathy has occurred. It may also occur with large dietary protein intake. A major limitation of creatinine clearance is that its accuracy worsens in relation to the amount of tubular creatinine secretion. Often as GFR declines, the contribution of urine creatinine from tubular secretion increases, further increasing the discrepancy between true GFR and measured creatinine clearance. Estimated GFR: According to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group, chronic kidney disease (CKD) is defined as the abnormalities of kidney structure or function, present for more than 3 months, with implications for health.(1.2) CKD should be classified by cause, GFR category, and albuminuria category.(1.2) KDIGO guidelines provide the following GFR categories(1.2): Stage Terms GFR mL/min/1.73 m(2) G1 Normal or high 90 G2* Mildly decreased 60 to 89 G3a Mildly to moderately decreased 45 to 59 G3b Moderately to severely decreased 30-44 G4 Severely decreased 15-29 G5 Kidney failure <15 *In the absence of evidence of kidney damage, neither G1 nor G2 fulfill criteria for CKD. Urinary albumin excretion can also be used to further subdivide CKD stages.

Reference Values:
CREATININE CLEARANCE
Males:
- 0-18 years: Reference values have not been established
- 19-75 years: 77-160 mL/min/BSA
- > or =76 years: Reference values have not been established

Females:
0-17 years: Reference values have not been established
18-29 years: 78-161 mL/min/BSA
30-39 years: 72-154 mL/min/BSA
40-49 years: 67-146 mL/min/BSA
50-59 years: 62-139 mL/min/BSA
60-72 years: 56-131 mL/min/BSA
> or =73 years: Reference values have not been established

CREATININE, URINE:
Reported in units of mg/dL

CREATININE, SERUM
Males:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

eGFR
> or =60 mL/min/BSA
Estimated GFR calculated using the 2009 CKD_EPI creatinine equation

Clinical References:

Creatinine with Estimated GFR (CKD-EPI), Serum

Clinical Information: Creatinine: In muscle metabolism, creatinine is synthesized endogenously from creatine and creatine phosphate. Creatinine is removed from plasma by glomerular filtration into the urine without being reabsorbed by the tubules to any significant extent. Renal tubular secretion also contributes a small quantity of creatinine to the urine. As a result, creatinine clearance often overestimates the true glomerular filtration rate (GFR) by 10% to more than 20%. Determinations of creatinine and renal clearance of creatinine are of value in the assessment of kidney function. Serum or blood creatinine levels in renal disease generally do not increase until renal function is substantially impaired. Estimated glomerular filtration rate (eGFR): eGFR is calculated using the 2009 chronic kidney disease (CKD) epidemiology collaboration (CKD-EPI) equation: eGFR (CKD-EPI) = 141 x min(Scr/k, 1)alpha x max(Scr/k,1)-1.209 x 0.993age x 1.018 (if patient is female) x 1.159 (if patient is black) -where age is in years -k is 0.7 for females and 0.9 for males -alpha is -0.329 for females and -0.411 for males -min indicates the minimum of Scr/k or 1 -max indicates the maximum of Scr/k or 1. Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with CKD and
those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Reasons given for routine reporting of eGFR with every serum creatinine in adult (18 and over) patients include: -GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age, sex, and, to a lesser extent, race, on creatinine production further cloud interpretation. -Creatinine is commonly measured in routine clinical practice. Albuminuria (>30 mg/24 hour or urine albumin to creatinine ratio >30mg/g) may be a more sensitive marker of early renal disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. -Monitoring of kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. -The CKD-EPI equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m\(^2\)) using sex, age, and race. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The CKD-EPI equation does require race (African American or non-African American), which also may not be readily available. For this reason, eGFR values for both African Americans and non-African Americans are reported. The difference between the 2 estimates is typically about 20%. The patient or provider can decide which result is appropriate for a given patient. The Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group clinical practice guideline,(2) as further defined by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary,(3) provide the following recommendations for reporting and interpretation of serum creatinine and eGFR: 1.4.3: Evaluation of GFR -1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (1A) 1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (2B) 1.4.3.3: We recommend that clinicians (1B): -Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone. -Understand clinical settings in which eGFRcreat is less accurate. 1.4.3.4: We recommend that clinical laboratories should (1B): -Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology. -Report eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat. -Report eGFRcreat in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation. When reporting serum creatinine: -We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (mmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dl). When reporting eGFRcreat: -We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m\(^2\) in adults using the units ml/min/1.73 m\(^2\). - We recommend eGFRcreat levels less than 60 ml/min/1.73 m\(^2\) should be reported as "decreased". 1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions (2B)

**Useful For:** Creatinine: -Diagnosing and monitoring treatment of acute and chronic renal diseases -Adjusting dosage of renally excreted medications -Monitoring renal transplant recipients Estimated Glomerular Filtration Rate (eGFR): Serum creatinine measurement is used in estimating GFR for people with chronic kidney disease (CKD) and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease)

**Interpretation:** Creatinine: Because serum creatinine is inversely correlated with glomerular filtration rate (GFR), when renal function is near normal, absolute changes in serum creatinine reflect larger changes than do similar absolute changes when renal function is poor. For example, an increase in serum creatinine from 1 to 2 mg/dL may indicate a decrease in GFR of 50 mL/min (from 100 to 50 mL/min), whereas an increase in serum creatinine level from 4 to 5 mg/dL may indicate a decrease of only 5 mL/min (from 25 to 20 mL/min). Because of the imprecision of serum creatinine as an assessment of GFR, there may be clinical situations where a more accurate GFR assessment must be
performed, iothalamate or inulin clearance are superior to serum creatinine and eGFR. Several factors may influence serum creatinine independent of changes in GFR. For instance, creatinine generation is dependent upon muscle mass. Thus, young, muscular males may have significantly higher serum creatinine levels than elderly females, despite having similar GFRs. Also, because some renal clearance of creatinine is due to tubular secretion, drugs that inhibit this secretory component (eg, cimetidine and trimethoprim) may cause small increases in serum creatinine without an actual decrease in GFR.

Estimated GFR: According to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group, chronic kidney disease (CKD) is defined as the abnormalities of kidney structure or function, present for more than 3 months, with implications for health.(3,4) CKD should be classified by cause, GFR category, and albuminuria category.(3,4) KDIGO guidelines provide the following GFR categories(2,3): Stage Terms GFR mL/min/1.73 m(4) G1* Normal or high 90 G2* Mildly decreased 60 to 89 G3a Mildly to moderately decreased 45 to 59 G3b Moderately to severely decreased 30-44 G4 Severely decreased 15-29 G5 Kidney failure <15 *In the absence of evidence of kidney damage, neither G1 nor G2 fulfill criteria for CKD.

Reference Values:

CREATININE

Males(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10years: 0.26-0.61 mg/dL
11-14years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL(2)

Females(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10years: 0.26-0.61 mg/dL
11-15years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL(2)

ESTIMATED GFR
> or =60 mL/min/BSA

Note: eGFR results will not be calculated for patients <18 years old.


Creatinine, 24 Hour, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus the amount of creatinine produced is, in large part, dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate.

Useful For: Calculation of creatinine clearance, a measure of renal function, when used in conjunction
with serum creatinine

**Interpretation:** Twenty-four-hour urinary creatinine determinations are principally used for the calculation of creatinine clearance. Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease or result from adverse effects on renal hemodynamics, which are often reversible, including certain drug usage or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

**Reference Values:**
Reference values mg per 24 hours:
- Males > or =18 years: 930-2955 mg/24 hours
- Females > or =18 years: 603-1783 mg/24 hours

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

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

**Clinical References:**

**Cortisol, 24 Hour, Urine**

**Clinical Information:** Urinary cortisol is a metabolite of circulating cortisol. As such, it is considered an indirect measure of adrenal glucocorticoid production. It is not protein-bound and is freely filtered by glomeruli. All of the filtered cortisol is excreted in the urine. Renal tubular secretion of cortisol also contributes to a small proportion of excreted cortisol. Although most excreted cortisol is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary cortisol levels. The renal clearance of cortisol provides an estimate of glomerular filtration rate.

**Useful For:** Urinary cortisol, in conjunction with serum cortisol, is used to calculate the cortisol clearance, a measure of adrenal function. Normalizing urinary analytes to account for the variation in urinary concentration.

**Interpretation:** Decreased cortisol clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effects on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased cortisol clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It may also occur with large dietary protein intake.

**Reference Values:**
Only orderable as part of a profile. For more information see:
- NMH24 / N-Methylhistamine, 24 Hour, Urine
- RBP24 / Retinol-Binding Protein, 24 Hour, Urine

Normal values mg per 24 hours:
- Males: 930-2955 mg/24 hours
- Females: 603-1783 mg/24 hours
Reference values have not been established for patients who are less than 18 years of age. 

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

**Clinical References:**

**Creatinine, Body Fluid**

**Clinical Information:** Byproducts of nitrogen metabolism are present in high concentration in urine compared to blood and serve as a surrogate marker for the identification of urine leakage into a body compartment. Concentrations of creatinine or urea nitrogen that exceed the concentration found in a concurrent sample of blood are suggestive of the presence of urine.(1) Peritoneal, abdominal, pelvic drain fluid: Trauma as well as abdominal or pelvic surgery can lead to bladder perforation or formation of urinary fistula with excessive accumulation of peritoneal fluid or increased surgical drain output caused by intraperitoneal urinary leakage.(1,2) Pleural fluid: Urinoma describes the accumulation of urine in the perirenal and retroperitoneal spaces caused by genitourinary tract injury due to trauma or blockage of the urinary tract due to stones, strictures, tumors, benign prostate hypertrophy, etc.(3) Rarely, this fluid can translocate to the pleural cavity causing pleural effusion via movement of urine through the diaphragm or via lymphatic communication between retroperitoneal and pleural spaces caused by increased pressure due to urinoma. Urinorthorax is the term used to describe an accumulation of urine in the pleural space. Patients often develop symptoms of dyspnea, chest pain, abdominal pain, and reduced diuresis.(4) The condition is reversed when treatment is directed to correct the primary cause (trauma in 75% and obstruction in 24% of cases). The pleural fluid to serum creatinine ratio is above 1 in 97.9% of cases (n=48; median ratio=2.9, range=0.95-16). Peritoneal dialysis fluid: Peritoneal dialysis (PD) is a type of ambulatory dialysis in which hyperosmotic fluid is infused into the patient's peritoneal cavity, with the peritoneum employed as the dialysis membrane promoting the diffusion of small molecules and free water from circulation.(5) The peritoneal equilibration test estimates the rate of small solute transport across the peritoneal membrane and the ultrafiltration capacity. Several analytes may be measured in order to perform this test. Creatinine is measured in PD fluid as well as in plasma or serum in samples taken 2 and/or 4 hours after the dialysate is instilled. The dialysate fluid to serum or plasma creatinine ratio is calculated with larger ratios (approaching 1.0) observed in patients exhibiting faster transport rates.

**Useful For:** Identifying the presence of urine as a cause for accumulation of fluid in a body compartment Measuring the ultrafiltration capacity of the peritoneal membrane in patients receiving peritoneal dialysis

**Interpretation:** Peritoneal, pleural, and drain fluid concentrations should be compared to serum or plasma. Fluid to serum ratios above 1.0 suggest the specimen may be contaminated with urine.(1-4) Peritoneal dialysate fluid to serum creatinine ratios can be calculated from timed collections to determine peritoneal membrane transport rates.(5) All other fluids: results should be interpreted in conjunction with serum creatinine and other clinical findings.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Creatinine, Random, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate. Since creatinine, for the most part, in the urine only comes from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

Useful For: Calculation of creatinine clearance, a measure of renal function, when used in conjunction with serum creatinine Normalization of urinary analytes by creatinine concentration to account for the variation in urinary concentrations between subjects

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effects on renal hemodynamics, which are often reversible including certain drugs or from decreases in effective renal perfusion (e.g., volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
> or =18 years old: 16-326 mg/dL

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

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
Only orderable as part of a profile. For more information see:
- NMHR / N-Methylhistamine, Random, Urine
- F2ISO / F2-Isoprostanes, Random, Urine
- ROXUR / Oxalate, Random, Urine
- CITRA / Citrate Excretion, Random, Urine
- RPHOS / Phosphorus, Random, Urine
- CACR3 / Calcium/Creatinine Ratio, Random, Urine
- MAGRU / Magnesium/Creatinine Ratio, Random, Urine
- RURCU / Uric Acid Random, Urine
- RTRP2 / Tubular Phosphorus Reabsorption, Random
- RMA / Microalbumin Random, Urine
- ALBR / Albumin, Random, Urine
- COUO / Cobalt Occupational Exposure, Random, Urine
- CRCRU / Chromium/Creatinine Ratio, Random, Urine
- CRUO / Chromium Occupational Exposure, Random, Urine
- RPTU1 / Protein/Creatinine Ratio, Random, Urine
- CARU / Cyclic Adenosine Monophosphate (cAMP), Urinary Excretion, Serum and Urine

16-326 mg/dL
Reference values have not been established for patients who are less than 18 years of age.

hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (e.g., volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

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

Not applicable

**Clinical References:**

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**Cryoglobulin and Cryofibrinogen Panel, Serum and Plasma**

**Clinical Information:** Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins are classified as: -Type I (monoclonal) -Type II (mixed--2 or more immunoglobulins of which 1 is monoclonal) -Type III (polyclonal--in which no monoclonal protein is found) Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia. A cryoprecipitate that is seen in plasma but not in serum is caused by cryofibrinogen. Cryofibrinogens are extremely rare and can be associated with vasculitis. Due to the rarity of clinically significant cryofibrinogenemia, testing for cryoglobulins is usually sufficient for investigation of cryoproteins.

**Useful For:** Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure This test is not useful for general screening of a population without a clinical suspicion of cryoglobulinemia.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**

**CRYOGLOBULIN**
Negative (positives reported as percent or trace amount)
If positive after 1 or 7 days, immunotyping of the cryoprecipitate is performed at an additional charge.

**CRYOFIBRINOGEN**
Negative
Quantitation and immunotyping will not be performed on positive cryofibrinogen.

**Clinical References:**
**CRY_S**

**Cryoglobulin, Serum**

**Clinical Information:** Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins are classified as: -Type I (monoclonal) -Type II (mixed--2 or more immunoglobulins of which 1 is monoclonal) -Type III (polyclonal--in which no monoclonal protein is found) Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia.

**Useful For:** Evaluating cryoglobulins in patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases Evaluating cryoglobulins in patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure This test is not useful for general screening of a population without a clinical suspicion of cryoglobulinemia.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Negative (positives reported as percent or trace amount)
If positive after 1 or 7 days, immunotyping of the cryoprecipitate is performed at an additional charge.

**Clinical References:**

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**SLFA**

**Cryptococcus Antigen Screen with Titer, Serum**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoforms or Cryptococcus gattii. C neoforms has been isolated from several sites in nature, particularly weathered pigeon droppings. C gatti was previously associated with tropical and subtropical regions only; however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoforms infections occur in immunocompromised patient populations, C gattii is has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** Aiding in the diagnosis of cryptococcosis This test should not be used as a test of cure or...
to guide treatment decisions. This test should not be used as a screening procedure for the general populations.

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay screen are automatically repeated with the same method utilizing dilutions in order to generate a titer value. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

**Reference Values:**
Negative

**Clinical References:**

**Cryptococcosis Antigen Screen with Titer, Spinal Fluid**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. Cryptococcus neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously associated with tropical and subtropical regions only, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis, which test positive by the lateral flow assay, should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

**Useful For:** Aiding in the diagnosis of cryptococcosis This test should not be performed as a screening procedure for the general population. This test should not be used as a test of cure or to guide treatment decisions.

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions in order to generate a titer
value. CSF specimens submitted for initial diagnosis, which test positive by LFA, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

Reference Values:
Negative
Reference values apply to all ages.

Clinical References:

Cryptococcus Antigen Screen, Lateral Flow Assay, Pleural Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously associated with tropical and subtropical regions only; however, more recently this organism has also been found to be endemic in British Columbia, along the Pacific Northwest, and in the Southeastern United States. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Diagnosis of infection with Cryptococcus species

Interpretation: The presence of cryptococcal antigen in pleural fluid is indicative of infection with Cryptococcus species. Monitoring cryptococcal antigen levels as a means to determine response to therapy is discouraged, as antigen levels may persist despite adequate treatment and disease resolution. A negative result indicates lack of infection; however, rare cases of false-negative results have been reported. Fungal culture should always be ordered alongside antigen testing.

Reference Values:
Negative

Clinical References:
1. Binnicker MJ, Jespersen DJ, Bestrom JE, Rollins LO: Comparison of four
Cryptococcus Antigen Screen, Lateral Flow Assay, Urine

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in HIV-infected patients. Mortality associated with CNS cryptococcosis approaches 25% despite antifungal therapy, while untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of infection with Cryptococcus neoformans or Cryptococcus gattii. This test should not be used as a test of cure. This test should not be used as a screening procedure for the general population.

Interpretation: The presence of cryptococcal antigen (CrAg) in any body fluid is strongly suggestive of infection with Cryptococcus neoformans or Cryptococcus gattii. Declining titers are suggestive of clinical response to therapy. However, monitoring CrAg titers should not be used as a test of cure, as low level titers may persist for extended periods of time following appropriate therapy and disease resolution. In addition to testing for CrAg, patients with presumed disease due to C neoformans or C gattii should have appropriate clinical specimens (eg, blood, bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References:

Cryptococcus Antigen Titer, Lateral Flow Assay, Pleural Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously associated with tropical and subtropical regions only; however, more recently this organism has also been found to be endemic in British Columbia, along the Pacific Northwest and in the Southeastern United States. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in
Cryptococcus Antigen Titer, Lateral Flow Assay, Serum

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C. neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C. gattii was previously associated with tropical and subtropical regions only, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States and is associated with several different tree species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C. neoformans infections occur in immunocompromised patient populations, C. gattii has a higher predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** Monitoring Cryptococcus antigen titers in serum

**Aiding in the diagnosis of cryptococcosis**

**This test should not be used as a test of cure or to guide treatment decisions.**

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.

**Reference Values:** Negative

Cryptococcus Antigen Titer, Lateral Flow Assay, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. Cryptococcus neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C. gattii was previously associated with tropical and subtropical regions only, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C. neoformans infections occur in immunocompromised patient populations, C. gattii is has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis that test positive by the lateral flow assay should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

Useful For: Monitoring Cryptococcus antigen titers in cerebrospinal fluid Aiding in the diagnosis of cryptococcosis This test should not be used as a test of cure or to guide treatment decisions.

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4) CSF specimens submitted for initial diagnosis that test positive by the lateral flow assay, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured.

Reference Values:
Negative

Clinical References:
Cryptococcus Antigen Titer, Lateral Flow Assay, Urine

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in HIV-infected patients. Mortality associated with CNS cryptococcosis approaches 25% despite antifungal therapy, while untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of infection with Cryptococcus neoformans or Cryptococcus gattii. This test should not be used as a test of cure.

Interpretation: The presence of cryptococcal antigen (CrAg) in any body fluid is strongly suggestive of infection with Cryptococcus neoformans or Cryptococcus gattii. Declining titers are suggestive of clinical response to therapy. However, monitoring CrAg titers should not be used as a test of cure, as low level titers may persist for extended periods of time following appropriate therapy and disease resolution. In addition to testing for CrAg, patients with presumed disease due to C neoformans or C gattii should have appropriate clinical specimens (eg, blood, bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

Reference Values: Only orderable as a reflex. For more information see ULFA / Cryptococcus Antigen Screen, Lateral Flow Assay, Urine.


Cryptococcus Antigen with Reflex, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis, which test positive by the lateral flow assay, should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

Useful For: Aiding in the diagnosis of cryptococcosis. This test should not be used as a test of cure or to guide treatment decisions. This test should not be performed as a screening procedure for the general population.
**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions in order to generate a titer value. CSF specimens submitted for initial diagnosis, which test positive by LFA, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.

**Reference Values:**

**CRYPTOCOCCUS ANTIGEN SCREEN WITH TITER**
- Negative
  - Reference values apply to all ages.

**CRYPTOCOCCUS ANTIGEN TITER, LFA**
- Negative
  - Reference values apply to all ages.

**FUNGAL CULTURE**
- Negative
  - If positive, fungus will be identified.
  - Reference values apply to all ages.

**Clinical References:**

**Cryptosporidium Antigen, Feces**

**Clinical Information:** Cryptosporidia are small apicomplexan protozoan parasites that infect the intestinal tract of humans and animals. They were conventionally categorized as coccidia, but are now known to be more closely related to the gregarines. Many species may infect humans, with the most common beingCryptosporidium hominis and C.parvum. Infected humans and animals shed small (4-6 micrometer in diameter) infectious oocysts in their stool, and these can subsequently contaminate and survive in recreational and drinking water supplies. Infection of humans occurs by the fecal-oral route or via ingestion of contaminated water or food. Infection is easily acquired, with an infectious dose of approximately 100 oocysts. Waterborne transmission is a primary mode of transmission and is commonly responsible for human outbreaks. This is due to the fact that Cryptosporidium species oocysts are resistant to cold temperatures and chlorine, and require extensive filtration or water treatment to remove them from drinking water. The incubation period is typically 7 to 10 days following exposure. While most patients have symptoms, approximately 30% of infected individuals are asymptomatic. When symptoms are present, they usually include profuse watery diarrhea, malaise,
anorexia, nausea, crampy abdominal pain, and low grade fever. Infection is usually self-limited in
immunocompetent individuals, with resolution of symptoms in 10 to 14 days. However, diarrhea can be
prolonged and life-threatening in immunocompromised patients such as those with AIDS, infants, and
the elderly, and result in severe dehydration and wasting. The fecal ova and parasite examination is an
insensitive method for detecting Cryptosporidium, given the small size of the oocysts and their lack of
trichrome staining. Instead, use of the Cryptosporidium antigen test (CRYPS / Cryptosporidium
Antigen, Feces) or the multiplex gastrointestinal PCR panel (GIP / Gastrointestinal Pathogen Panel,
PCR, Feces) is recommended for sensitive and specific detection. The antigen test is ideal for situations
in which cryptosporidiosis is highly suspected (eg outbreak scenarios), whereas the PCR panel allows
for simultaneous detection of multiple parasitic, viral, and bacterial causes of diarrhea. See Parasitic
Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea
in Special Instructions for more information about diagnostic tests that may be of value in evaluating
patients with diarrhea.

**Useful For:** Establishing the diagnosis of intestinal cryptosporidiosis

**Interpretation:** A positive enzyme-linked immunosorbent assay (ELISA) indicates the presence of
antigens of cryptosporidium and is interpreted as evidence of infection with that organism. The
sensitivity, specificity, and positive predictive value of the ELISA were 87%, 99%, and 98%,
respectively, as determined by examination of 231 fecal specimens by conventional microscopy and by
ELISA.

**Reference Values:**
Negative

**Clinical References:** Centers for Disease Control and Prevention: Parasites-Cryptosporidium (also

**SFC**

8719

**Crystal Identification, Synovial Fluid**

**Clinical Information:** Birefringent crystals are found in the synovial fluid of more than 90% of
patients with acutely inflamed joints. Monosodium urate crystals are seen in gouty fluids and calcium
pyrophosphate crystals are seen in chondrocalcinosis. The urates are usually needle-shaped, and the
calcium crystals are often rhomboidal. Cholesterol crystals may also be observed.

**Useful For:** Identifying the presence and type of crystals in synovial fluid

**Interpretation:** Positive identification of crystals provides a definitive diagnosis for joint disease.

**Reference Values:**
None seen
   If present, crystals are identified.

ASCP Press 2015

**CSF3R**

64604

**CSF3R Exon 14 and 17 Mutation Detection by Sanger Sequencing, Varies**

**Clinical Information:** CSF3R encodes the receptor for colony-stimulating factor 3, a cytokine that
controls the production, differentiation, and function of granulocytes. Somatic CSF3R mutations were
recently described in 50% to 80% of chronic neutrophilic leukemia (CNL) patients. Their association with
atypical chronic myelogenous leukemia (aCML) remains controversial. They have also been reported as
somatic events in severe congenital neutropenia (SCN) patients. There are 2 types of CSF3R mutations:
extracellular domain/membrane proximal point mutations (most commonly p.T618I) and cytoplasmic tail
truncation mutations. They demonstrated sensitivity to JAK kinase inhibitors and Src kinase inhibitors,
respectively, in in vitro assays. In CNL, the most common mutation is p.T618I, although cytoplasmic
truncation mutation can also occur. Somatic cytoplasmic truncation mutations have been reported in
approximately 30% of SCN patients and 80% of SCN patients with leukemic transformation, who are often on granulocyte-colony stimulating factor (GCSF) therapy. However, their role in leukemic transformation is uncertain.

**Useful For:** Evaluation and classification of chronic neutrophilia. Aids in the diagnosis of chronic neutrophilic leukemia (CNL). Identification of mutations that may suggest the class of kinase inhibitor to which the neoplasm may be sensitive.

**Interpretation:** The results will be given as positive or negative for CSF3R mutation and, if positive, the mutation will be described.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
4. Vandenberghhe P, Beel K: Severe congenital neutropenia, a genetically heterogeneous disease group with an increased risk of AML/MDS. Pediatr Rep 2011;3(s2):e9

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**CU (Chronic Urticaria) Index Panel**

**Reference Values:**

- Anti-Thyroid Peroxidase IgG: < 35 IU/mL
- Anti-Thyroglobulin IgG: < 40 IU/mL
- TSH (Thyrotropin): 0.4 to 4.0 uIU/mL
- CU Index: < 10.0

The CU Index test is the second generation Functional Anti-FceR test. Patients with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease.

---

**CU Index**

**Clinical Information:** Patients with a chronic form of urticaria who are positive (> 10) with the CU index have an autoimmune basis for their disease. A positive result does not indicate which autoantibody (anti-IgE, anti-FceRI or anti-FCERII) is present.

**Reference Values:**

- < 10.0

The CU Index test is the second generation Functional Anti-FceR test. Patient with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease.

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**Cucumber IgG**

**Interpretation:**

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

**CUKE 82861**

**Cucumber, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cucumber Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**OATC 82916**

**Cultivated Oat, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cultivated oat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>1</td>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Cultivated Rye, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to cultivated rye Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>Strongly positive</td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


WHTC 82915

Cultivated Wheat, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to cultivated wheat

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

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</tr>
</tbody>
</table>
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


### Culture for Genetic Testing, Amniotic Fluid

**Clinical Information:** Fetal cells obtained by amniocentesis (amniocytes) are used for a wide range of laboratory tests. Prior to testing, the cells may need to be cultured to obtain adequate numbers of amniocytes.

**Useful For:** Producing amniocyte cultures that can be used for genetic analysis

**Reference Values:** Not applicable


### Culture for Genetic Testing, Tumor Tissue

**Clinical Information:** Cultured tumor cells can be used for a wide range of laboratory tests. Prior to testing, the tumor tissue will be cultured to obtain viable cells for genetic testing.

**Useful For:** Producing tumor cell cultures that can be used for genetic analysis

**Interpretation:** Once confluent flasks are established, the tumor cell cultures are sent to other laboratories, either within Mayo Clinic or to external sites, based on the specific testing requested.

**Reference Values:** Not applicable


### Culture Referred for Identification, Fungus

**Clinical Information:** Organisms are referred for identification or to confirm an identification made elsewhere. This may provide helpful information regarding the significance of the organism, its role in the disease process, and its possible origin.

**Useful For:** Identification of pure isolates of filamentous fungi and yeast

**Interpretation:** Genus and species are reported on fungal isolates whenever possible.

**Reference Values:** Not applicable

**Culture Referred for Identification, Mycobacterium and Nocardia with Antimicrobial Susceptibility Testing, Varies**

**Clinical Information:** There are nearly 200 recognized species of mycobacteria and more than 100 Nocardia species. Many are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, there are other aerobic actinomycete genera that can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Nucleic acid hybridization probes are utilized that identify specific ribosomal RNA sequences of Mycobacterium tuberculosis complex, Mycobacterium avium complex, and Mycobacterium gordonae. Other Mycobacteria species, Nocardia species, and other aerobic actinomycete genera are identified using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI TOF MS) or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene. After identification, antimicrobial susceptibility testing is performed following Clinical and Laboratory Standards Institute (CLSI) M24 guidelines using either broth dilution or critical concentration methods as appropriate for the species.

**Useful For:** Rapid identification to the species level and susceptibility testing for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates.

**Interpretation:** Organisms growing in pure culture are identified to the species level whenever possible.

**Reference Values:**
Not applicable

**Clinical References:**

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**Culture Referred for Identification, Mycobacterium and Nocardia, Varies**

**Clinical Information:** There are approximately 200 recognized species of mycobacteria and more than 100 Nocardia species. Many of these species are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, there are other aerobic actinomycete genera that can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Nucleic acid hybridization probes are utilized that identify specific ribosomal RNA sequences of Mycobacterium tuberculosis complex, Mycobacterium avium complex, and Mycobacterium gordonae. Other Mycobacteria species, Nocardia species and other aerobic actinomycete genera are identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene.

**Useful For:** Rapid identification to the species level for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates.

**Interpretation:** Organisms growing in pure culture are identified to the species level whenever possible.

**Reference Values:**
Not applicable

**Clinical References:**
3. Caulfield AJ,
Culture Referred for Identification, Virus

**Clinical Information:** Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus (CMV), enteroviruses, herpes simplex virus (HSV), influenza virus, parainfluenza virus (types 1-3), respiratory syncytial virus (RSV), and varicella-zoster virus (VZV). Some viral infections can be treated with antiviral drugs. Early laboratory diagnosis by isolation may be helpful in the medical management of these patients. Viruses that may be recovered in cell culture include adenovirus, CMV, enterovirus, HSV, VZV, RSV, influenza virus, and parainfluenza virus. HSV and enterovirus are the most commonly recovered viruses. A number of viruses are not routinely detected in cell culture. These include Epstein-Barr virus (EBV), rubella virus (must order serology), human papillomavirus (HPV), Norwalk or norovirus, and West Nile virus.

**Useful For:** Viral identification and confirmation

**Interpretation:** A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of the result. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by culture include Epstein-Barr virus, rubella virus, human papilloma virus, norovirus and West Nile virus), and nonviable organisms submitted. Parainfluenza virus type 4 also may not be detected by viral culture.

**Reference Values:**
Not applicable

**Clinical References:**

Curry, IgE, Serum

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


---

**Curvularia lunata, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Curvularia lunata - Defining the allergen responsible for eliciting signs and symptoms - Identifying allergens - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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

**Reference Values:**

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Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


Curvularia spicifera/Bipolaris IgE

Interpretation:  Class IgE (kU/L) Comment
0   <.10 Negative
0/1  0.10-0.34 Equivocal/Borderline
1   0.35-0.69 Low Positive
2   0.70-3.49 Moderate Positive
3   3.50-17.4 High Positive
4   17.50-49.9 Very High Positive
5   50.00-99.9 Very High Positive
6   >99.99 Very High Positive

Reference Values:
<0.35 kU/L

Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies

Clinical Information: This test can be used to customize genetic testing panels offered at Mayo Clinic Laboratories. Individual genes can be added or removed to an existing genetic testing panel. Additionally, this test can be used to create your own custom single gene or multi-gene panel or to combine existing panels within the same disease state. Note: any genes added to the custom panel must be from the same disease state. Only one Gene List ID may be submitted per Custom Gene Panel, Hereditary order. The Gene List ID can be created using the Custom Gene Ordering tool (see Ordering Guidance).

Useful For: Customization of existing next-generation sequencing (NGS) panels offered through Mayo Clinic Laboratories. Detection single nucleotide and copy number variants in a custom gene panel. Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for a hereditary condition.

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

Reference Values:
An interpretive report will be provided.

**Cutaneous Direct Immunofluorescence Assay (IFA), Varies**

**Clinical Information:** Skin or mucosal tissue from patients with autoimmune bullous diseases, connective tissue disease, vasculitis, lichen planus, and other inflammatory conditions often contains bound immunoglobulin, complement, or fibrinogen. Biopsy specimens are examined for the presence of bound IgG, IgM, IgA, third component of complement (C3), and fibrinogen.

**Useful For:** Confirming a diagnosis of bullous pemphigoid, cicatrical pemphigoid, pemphigoid gestationis and other variants of pemphigoid, all types of pemphigus, including paraneoplastic pemphigus (paraneoplastic multiorgan syndrome), dermatitis herpetiformis, linear IgA bullous dermatosis, chronic bullous disease of childhood, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous eruption of lupus erythematosus, and atypical or mixed forms of bullous disease, systemic lupus erythematosus, cutaneous lupus erythematosus, or other variants, vasculitis, lichen planus, and other inflammatory diseases. This test is not useful for diagnosis of malignancies involving the skin.

**Interpretation:** A board-certified Dermatopathologist will review and interpret the test results in correlation with other clinical findings as provided.

**Reference Values:**
Report includes description and interpretation of staining patterns.

**Clinical References:**

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**Cutaneous Immunofluorescence Antibodies (IgG), Serum**

**Clinical Information:** IgG anti-basement zone (BMZ) antibodies are produced by patients with pemphigoid. In most patients with bullous pemphigoid, serum contains IgG anti-BMZ antibodies, while in cicatrical pemphigoid circulating IgG anti-BMZ antibodies are found in a minority of cases. Sensitivity of detection of anti-BMZ antibodies is increased when serum is tested using sodium chloride (NaCl)-split human skin as substrate. Circulating IgG anti-BMZ antibodies are also detected in patients with epidermolysis bulbosa acquisita (EBA) and bullous eruption of lupus erythematosus. IgG anti-cell surface (CS) antibodies are produced by patients with pemphigus. The titer of anti-CS antibodies generally correlates with disease activity of pemphigus.

**Useful For:** Confirming a diagnosis of pemphigoid, pemphigus, epidermolysis bulbosa acquisita, or bullous lupus erythematosus.

**Interpretation:** Indirect immunofluorescence (IF) testing may be diagnostic when histologic or direct IF studies are only suggestive, nonspecific, or negative. Anti-cell surface (CS) antibodies correlate with a diagnosis of pemphigus. Anti-basement zone (BMZ) antibodies correlate with a diagnosis of bullous pemphigoid, cicatrical pemphigoid, epidermolysis bulbosa acquisita (EBA), or bullous eruption of lupus erythematosus (LE). If serum contains anti-BMZ antibodies, the pattern of fluorescence on sodium chloride(NaCl)-split skin substrate helps distinguish pemphigoid from EBA and bullous LE. Staining of the roof (epidermal side) or both epidermal and dermal sides of NaCl-split skin correlates with the diagnosis of pemphigoid, while fluorescence localized only to the dermal side of the split-skin substrate correlates with either EBA or bullous LE.

**Reference Values:**
Report includes presence and titer of circulating antibodies. If serum contains BMZ antibodies on split-skin substrate, patterns will be reported as: 1) epidermal pattern, consistent with pemphigoid or 2) dermal pattern, consistent with epidermolysis bulbosa acquisita.
Negative in normal individuals


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**CXCL13 Immunostain, Technical Component Only**

**Clinical Information:** CXCL13 (CXC motif chemokine ligand 13) is useful in the classification of nodal T-cell lymphomas with T-follicular helper (TFH) phenotype, and the diagnosis of follicular dendritic cell sarcoma.

**Useful For:** Assessment of CXCL13 (CXC motif chemokine ligand 13) expression

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CXCR4 Mutation Analysis, Somatic, Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, Varies**

**Clinical Information:** Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes, and spleen. It is a B-cell neoplasm that can exhibit excess production of serum IgM symptoms related to hyperviscosity, tissue filtration, and autoimmune-related pathology. CXCR4 variants are identified in approximately 30% to 40% of LPL/WM patients and are almost always associated with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 variants in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib. A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift variants) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients. A MYD88-L265P/CXCR4-WT (wild type) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients. A MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 variant.

**Useful For:** Aiding in the prognostication and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

**Interpretation:** Variants detected or not detected. An interpretive report will be issued.
Reference Values:
Variants present or absent in the test region of the CXCR4 gene (NCBI NM_003467.2, GRCh37).


FCYNB Cyanide, Blood Test

Reference Values:
Normal: Up to 0.05 mcg/mL
Potentially toxic: 0.50 mcg/mL and greater
Potentially lethal: 2.0 mcg/mL and greater

CARU Cyclic Adenosine Monophosphate (cAMP), Urinary Excretion, Serum and Urine

Clinical Information: Adenosine cyclic 3',5'-monophosphate (cAMP) functions as an intracellular "second messenger" regulating the activity of intracellular enzymes or proteins in response to a variety of hormones (eg, parathyroid hormone). Urinary cAMP is elevated in about 85% of patients with hyperparathyroidism.

Useful For: Differential diagnosis of hypercalcemia Adjunct to serum parathyroid hormone measurements, especially in the diagnosis of parathyroid hormone resistance states, such as pseudohypoparathyroidism

Interpretation: Urinary adenosine cyclic 3',5'-monophosphate (cAMP) is elevated in about 85% of patients with hyperparathyroidism and in about 50% of patients with humoral hypercalcemia of malignancy.

Reference Values:
CYCLIC AMP
1.3-3.7 nmol/dL of glomerular filtrate

CREATININE, SERUM
Males
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 786
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

CREATININE, URINE
No reference values apply. Interpret with other clinical data.


Cyclic Citrullinated Peptide Antibodies, IgG, Serum

Clinical Information: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic joint inflammation that ultimately leads to joint destruction. RA affects approximately 1% of the world's population. The diagnosis of RA is established primarily on clinical criteria and serologic findings. Historically, rheumatoid factor (RF), which is an antibody specific for the Fc portion of human IgG, has been considered a marker for RA. RF is, in fact, one of the diagnostic criteria for RA that was established by the American College of Rheumatology. Although 50% to 90% of patients with RA are RF-positive, the specificity of the RF test is known to be relatively poor. RF is found in many patients with other autoimmune diseases, infectious diseases and some healthy individuals. Consequently, a search for better diagnostic markers, with improved specificity for RA, ensued. Antiperinuclear factor (APF) and antikeratin antibodies (AKA), identified by immunofluorescence, were found to have a specificity of close to 90% for RA, but testing for these autoantibodies has never become popular. It was subsequently determined that APF and AKA react with the same antigen, specifically a citrullinated form of filaggrin (citru-line is an unusual amino acid formed by posttranslational modification of arginine residues by the enzyme peptidyl arginine deaminase). Recombinant filaggrin fragments, after enzymatic deamination in vitro, react with autoantibodies in RA sera. Synthetic cyclic citrullinated peptide (CCP) variants also react with anti-filaggrin autoantibodies and serve as the substrate for detecting anti-CCP antibodies serologically. Most studies of anti-CCP antibodies demonstrated that these autoantibodies have much improved specificity for RA compared to RF. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients suspected of having rheumatoid arthritis (RA) Differentiating RA from other connective tissue diseases that may present with arthritis

Interpretation: A positive result for cyclic citrullinated peptide (CCP) antibodies indicates a high likelihood of rheumatoid arthritis (RA). A Mayo prospective clinical evaluation of the CCP antibody test showed a diagnostic sensitivity for RA of 78% with fewer than 5% false positive results in healthy controls (see Cautions). CCP antibodies have also been reported in approximately 40% of seronegative RA patients, and, like rheumatoid factor (RF), a positive CCP antibody result indicates an increased likelihood of erosive disease in patients with RA. High levels of CCP antibodies may be useful to identify patients with aggressive disease, but further studies are needed to document this association. The level of CCP antibodies may also correlate with disease activity in RA, but further studies are needed to document this clinical application.

Reference Values:
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-59.9 U (positive)
> or =60.0 U (strong positive)
Reference values apply to all ages.


**CYC1**

**Cyclin D1 Immunostain, Technical Component Only**

**Clinical Information:** Cyclin D1 is a protein that regulates entry of the cell into cell cycle. It drives the transition between G0 and G1 phase. In normal tissues, basal epithelial cells, endothelial cells, and stromal cells are often cyclin D1 positive. As a result of a translocation involving the cyclin D1 gene and IgH, t(11;14), the vast majority of mantle cell lymphomas overexpress cyclin D1. This is a useful feature in the classification of low-grade B-cell lymphomas.

**Useful For:** Classification of low-grade B-cell lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FFLEX**

**Cyclobenzaprine (Flexeril)**

**Reference Values:**

Reference Range: 10 - 30 ng/mL

**CYCL**

**Cyclospora Stain, Feces**

**Clinical Information:** Cyclospora cayetanensis is an apicomplexan protozoan parasite that causes watery diarrhea, anorexia, malaise, and weight loss. The extent of symptoms depends on the age and condition of the host and the infectious dose. The infection is usually self-limited, but symptoms can be severe and prolonged, particularly in immunocompromised patients. Cyclosporal diarrheal disease is endemic in many parts of the world, including Asia, India, Southeast Asia, and Latin America. Although most cases of cyclosporiasis have been seen in travelers to developing countries, outbreaks in the United States have been noted due to contaminated fruits and vegetables from Latin America. Transmission is via fecally contaminated food or water. If untreated, symptoms typically last for 10 to 12 weeks, and may follow a relapsing course. The infection usually responds to treatment with a sulfamethoxazole-trimethoprim drug combination. Cyclospora cayetanensis oocysts are traditionally detected by modified acid-fast staining, in which the oocysts stain bright pink-red. However, the modified safranin stain has been shown to provide increased sensitivity over modified acid-fast method and produces a more rapid result. It is the method used in our laboratory to detect Cyclospora cayetanensis oocysts in fecal sediment. See Laboratory Testing for Infectious Causes of Diarrhea and Parasitic Investigation of Stool Specimens Algorithm for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** The identification of Cyclospora cayetanensis as a cause of infectious gastroenteritis
**Interpretation:** A report of Cyclospora cayetanensis detected indicates the presence of this parasite in the patient's feces.

**Reference Values:**
Negative
If positive, reported as Cyclospora cayetanensis detected.

**Clinical References:**

**CYSPR 35143**

**Cyclosporine, Blood**

**Clinical Information:** Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by CYP3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis. Dose is adjusted initially (up to 2 months posttransplant) to maintain concentrations generally between 150 and 400 ng/mL. Target trough concentrations vary according to clinical protocol and depend on type of allograft, risk of rejection, concomitant immunosuppressive drugs, and toxicity. After the first 2 postoperative months, the target range is generally lower, between 75 and 300 ng/mL. Conversion between formulations is generally done at the same dose but with drug monitoring.

**Useful For:** Monitoring whole blood cyclosporine concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to cyclosporine with trough whole blood levels 100 to 400 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedinations. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next scheduled dose). Blood drawn at other times will yield higher results. This test may also be used to analyze cyclosporine levels 2 hours after dosing (C2 concentrations); trough therapeutic ranges do not apply to C2 specimens. The assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**
100-400 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

**Clinical References:**
**Cyclosporine, Peak, Blood**

**Clinical Information:** Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by CYP3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis.

**Useful For:** Monitoring whole blood cyclosporine concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers. Adjusting dose to optimize immunosuppression while minimizing toxicity. Evaluating patient compliance.

**Interpretation:** No definitive therapeutic or toxic ranges have been established for postdose peak monitoring. Preferred therapeutic ranges may vary by transplant type, protocol, and comedication. The 2-hour postdose cyclosporine ranges listed for this test are only suggested guidelines. This assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**

No definitive therapeutic or toxic ranges have been established.

Optimal blood drug levels are influenced by type of transplant, patient response, time posttransplant, coadministration of other drugs, and drug formulation.

The following 2-hour postdose cyclosporine ranges are only suggested guidelines:

- Renal transplant: 800-1700 ng/mL
- Liver transplant: 600-1000 ng/mL

Target steady-state peak concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

**Clinical References:**


**CYP2D6 3' Gene Duplication/Multiplication (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**CYP2D6 5' Gene Duplication/Multiplication (Bill Only)**

**Reference Values:**

This test is for billing purposes only.
This is not an orderable test.

**2D61Z CYP2D6 Full Gene Sequence (Bill Only)**

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

**2D62Z CYP2D6 Gene CYP2D6-2D7 Hybrid (Bill Only)**

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

**2D63Z CYP2D6 Gene CYP2D7-2D6 Hybrid (Bill Only)**

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

**2D64Z CYP2D6 Nonduplicated Gene (Bill Only)**

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

**CSTCE Cystatin C with Estimated Glomerular Filtration Rate (eGFR), Serum**

*Clinical Information:* Cystatin C is a low-molecular weight (13,250 kDa) cysteine proteinase inhibitor that is produced by all nucleated cells and found in body fluids, including serum. Since it is formed at a constant rate and freely filtered by the kidneys, its serum concentration is inversely correlated with the glomerular filtration rate (GFR); that is, a high concentration indicates a low GFR, while a lower concentration indicates a higher GFR, similar to creatinine. The renal handling of cystatin C differs from creatinine. While both are freely filtered by glomeruli, once filtered cystatin C, unlike creatinine, is reabsorbed and metabolized by proximal renal tubules. Therefore, under normal conditions, cystatin C does not enter the final excreted urine to any significant degree. The serum concentration of cystatin C is not greatly affected by body mass, age, sex, or race. Thus, in certain cases, cystatin C may be a more reliable marker of renal function (GFR) than creatinine. GFR can be estimated (eGFR) from serum cystatin C utilizing an equation that includes the age and sex of the patient. The CKD-EPI cystatin C equation was developed by Inker et al(1) and demonstrated good correlation with measured iothalamate clearance in patients with all common causes of kidney disease, including kidney transplant recipients. Cystatin C eGFR may have advantages over creatinine eGFR in certain patient groups in whom muscle mass is abnormally high or low (for example quadriplegics, much older adults, or malnourished individuals). Blood levels of cystatin C also equilibrate more quickly than creatinine, and therefore, serum cystatin C may be more accurate than serum creatinine when kidney function is rapidly changing (for example amongst hospitalized individuals).(2) The same group also developed an eGFR equation that uses serum creatinine and cystatin C, in addition to age, sex, and race.(1) This equation may be useful to average out potential confounders of creatinine versus cystatin C.

*Useful For:* Assessing renal function in patients suspected of having kidney disease Monitoring treatment response in patients with kidney disease An index of glomerular filtration rate (GFR),
especially in patients where serum creatinine may be misleading (eg, very obese, older adults, or malnourished patients) Calculation of CKD-EPI cystatin C estimated GFR for patients where serum creatinine may be misleading (eg, very obese, older adults, or malnourished patients)

**Interpretation:** Cystatin C: Cystatin C inversely correlates with the glomerular filtration rate (GFR), that is, elevated levels of cystatin C indicate decreased GFR. Cystatin C may provide more accurate assessment of GFR for very obese, older adults, or malnourished patients than creatinine. Cystatin C equation does not require patient ethnic data and can be used for those patients with this information unavailable. Due to immaturity of renal function, cystatin C levels are higher in neonates less than 3 months of age. (3) Estimated GFR: Chronic kidney disease (CKD) is defined as the presence of: persistent and usually progressive reduction in GFR (GFR <60 mL/min/1.73 m²) and/or albuminuria (>30 mg of urinary albumin per gram of urinary creatinine), regardless of GFR. According to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) classification, among patients with CKD, irrespective of diagnosis, the stage of disease should be assigned based on the level of kidney function(4) Stage Description GFR mL/min/BSA 1 Kidney damage with normal or increased GFR 90 2 Kidney damage with mild decrease in GFR 60-89 3A Mild to moderate decrease in GFR 45-59 3B Moderate to severe decrease in GFR 30-44 4 Severe decrease in GFR 15-29 5 Kidney failure <15 (or dialysis)

**Reference Values:**

Cystatin C:

- 18-49 years: 0.63-1.03 mg/L
- > or =50 years: 0.67-1.21 mg/L
- 0-17 years: Reference values have not been established. Refer to estimated glomerular filtration rate (eGFR).

Estimated GFR:

- >60 mL/min/BSA

Adult eGFR: Estimated GFR calculated using CKD-EPI Cystatin C equation.(1)

Pediatric eGFR: Estimated GFR calculated using Schwartz Cystatin C equation.(1)

**Clinical References:**

**Clinical Information:** Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. The incidence of CF varies markedly among different populations, as does the mutation detection rate for the mutation screening assay. To date, over 1,500 mutations have been described within the CF gene, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, deltaF508, accounts for approximately 67% of the mutations worldwide and approximately 70% to 75% in a North American Caucasian population. Most of the remaining mutations are rather rare, although some show a relatively higher prevalence in certain ethnic groups or in some atypical presentations of CF such as congenital bilateral absence of the vas deferens (CBAVD). Mutations detected by the assay performed in the Mayo Clinic Molecular Genetics Laboratory include the 23 mutations recommended by the American College of Medical Genetics as well as 83 other mutations. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least 1 copy of the G178R, G551S, G551D, S549N, S549R, G1244E, S1251N, S1255P, or G1349D mutation. The G178R, S549N, S549R, S551D, and S1251N mutations are included in this test. These 106 mutations account for approximately 91% of CF chromosomes in a Northern European Caucasian population. Detection rates for several ethnic and racial groups are listed in the table below. Note that interpretation of test results and risk calculations are also dependent on clinical information and family history. Racial or Ethnic Group Carrier Frequency Mutation Detection Rate* African American 1/65 81% Ashkenazi Jewish 1/25 97% Asian American (excluding individuals of Japanese ancestry) 1/90 54% Mixed European 1/25 82% Eastern European 1/25 77% French Canadian 1/25 91% Hispanic American 1/46 82% Northern European 1/25 91% Southern European 1/25 79% *Rates are for classical CF. Rates are lower for atypical forms of CF and for CBAVD. CFTR mutations listed below are included in this panel. Deletion exons 2-3 Exon 11: deltaF311 Exon 17a: C524X Exon 20: S1251N Intron 10: 1717+1G->A Exon 20: S1255X Exon 11: G542X Exon 20: 3905insT Exon 11: S549N Exon 20: W1282X (TGG->TGA) Exon 11: S549R (T->G) Exon 21: 4016insT Exon 11: G551D Exon 21: N1303K (C->A) Exon 11: Q552X Exon 21: N1303K (C->G) See Cystic Fibrosis Molecular Diagnostic Testing Algorithm in Special Instructions for additional information.

**Useful For:** Confirmation of a clinical diagnosis of cystic fibrosis Risk refinement via carrier screening for individuals in the general population Prenatal diagnosis or familial mutation testing when the familial mutations are included in the 106-mutation panel listed above (if familial mutations are not included in the 106-mutation panel, order FMTT / Familial Mutation, Targeted Testing) Risk refinement via carrier screening for individuals with a family history when familial mutations are not available Identification of patients who may respond to CFTR potentiator therapy

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

Cysticercosis Antibody, IgG, Serum

Clinical Information: Cysticercosis is caused by infection with Taenia solium, a tapeworm (cestode). In this form of infection, humans and pigs serve as the intermediate host and have the cystic larval form in their tissues. Humans can also serve as the definitive host for T solium and have the adult form in their intestine (known as taeniasis). Humans acquire cysticercosis by ingesting microscopic T solium eggs in contaminated food, water, or on fomites. The eggs enter the environment when they are shed in stool from a person with the intestinal form of infection; this could be the same patient (autoinfection) or a different patient. Once ingested, the eggs hatch in the intestine to release oncospheres, which invade the intestinal wall and disseminate via the blood to muscles, liver, brain, and other tissues where they form cysts (cysticerci). Taeniasis occurs when cysticerci are ingested in the undercooked flesh of an infected intermediate host (eg, pig). In the small intestine, cysticerci will evaginate and attach via a scolex to the intestinal wall. They then grow to become mature adult tapeworms. Adults can reside in the intestine for years and grow from 2 to 7 meters with over 500 proglottids, each filled with 50,000 eggs. While cysticercosis and taeniasis occur globally, in the United States, infections are predominantly encountered in immigrants from Latin and Central America who acquired the infection locally. The symptoms associated with cysticercosis depend on where the cysticerci localize, their size, number, and stage (degenerating, calcified, etc). The time between initial infection and symptom onset may vary from several months to years. The presence of cysts in the brain or spinal cord, referred to as neurocysticercosis, is the most serious form of disease and, while some individuals may be asymptomatic, many present with seizures (70%-90%), headache, confusion, and difficulty with balance. Cysts present in striated muscle are typically asymptomatic. Diagnosis of cysticercosis relies on both imaging studies and serologic testing results. Importantly, detection of T solium eggs or proglottids in stool by an ova and parasite exam is diagnostic for taeniasis, not cysticercosis. Individuals with taeniasis should be evaluated for cysticercosis by serology since autoinfection can occur. Due to imperfect sensitivity and specificity of commercially available enzyme-linked immunosorbent assays (ELISA) for cysticercosis, it is recommended that both positive and negative results by commercial ELISA be confirmed by a cysticercosis immunoblot offered through the Centers for Disease Control and Prevention (www.cdc.gov/dpdx/cysticercosis/index.html) for patients strongly suspected to have cysticercosis. Currently available antibody detection assays are unable to distinguish between active and inactive infections.

Useful For: Aiding in the diagnosis of infection with Taenia solium (cysticercosis)

Interpretation: Positive: Results suggest infection with Taenia solium (cysticercosis). Confirmatory testing through the Centers for Disease Control and Prevention is recommended. False-positive results may occur in patients with other helminth infections (eg, Echinococcus). Negative: No antibodies to Taenia solium (cysticercosis) detected. A negative result may not rule-out infection as the sample may have been collected prior to the development of a detectable level of antibodies. Sensitivity is negatively impacted by the presence of few cysticerci or location in areas less accessible to the immune system. Repeat testing on a new sample is recommended for patients at high risk of cysticercosis.

Reference Values:
Negative
Reference values apply to all ages.


**FCAEC 75587 Cysticercus Antibody (IgG), ELISA, CSF**

**Clinical Information:** Cysticercosis is caused by infection with the larval form (cysticercus) of the pork tapeworm, Taenia solium. A negative test result does not exclude the diagnosis of neurocysticercosis, particularly if only a single brain lesion is present. Test sensitivity increases from 50% or less for a solitary brain cyst to greater than 90% if 3 or more cysts are present. Antibodies from other parasitic infection, particularly results by the cysticercus IgG antibody Western blot is thus recommended.

**Reference Values:**
Reference Range: <0.75

Interpretive Criteria:
<0.75 Antibody Not Detected
> or =0.75 Antibody Detected

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecellary-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. Antibodies to other parasitic infections, particularly echinococcosis, may crossreact in the cysticercus IgG ELISA. Confirmation of positive ELISA results by the cysticercus IgG antibody Western blot is thus recommended.

**CYSGP 608027 Cystinuria Gene Panel, Varies**

**Clinical Information:** Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestines and kidneys. This leads to an accumulation of poorly soluble cystine and dibasic amino acids (lysine, arginine, and ornithine) in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7000. Cystinuria is an autosomal recessive disease, but some heterozygous carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically non-disease causing, urinary cystine and dibasic amino acid excretion. Some heterozygotes do tend to have higher levels of lysine and cystine versus arginine and ornithine as compared to patients with homozygous variants, who excrete large amounts of cysteine and all 3 dibasic amino acids. Cystinuria is caused by variants in genes, SLC3A1 and PREPL on chromosome 2p and SLC7A9 on chromosome 19q. Initially, the disease was classified into subtypes I, II, and III (type II and III are also referred as nontype-I) based on the amount of urinary cystine excreted in heterozygous parental specimens. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to variants in the SLC3A1 gene; type B, due to variants in the SLC7A9 gene; and type AB, due to 1 variant in each SLC3A1 and SLC7A9 gene. A contiguous gene deletion involving both SLC3A1 and PREPL gene is associated with an autosomal recessive hypotonia-cystinuria syndrome, presenting with dysmorphic features, severe neonatal hypotonia, myasthenic syndrome, failure to thrive in infancy with transition to hyperphagia in late childhood, and nephrolithiasis with excretion of cystine, lysine, arginine and ornithine. Variants in the PREPL gene is associated with autosomal recessive congenital myasthenic syndrome 22 (CMS22), which does not present with cystinuria. Urinary measurement of cystine, lysine, ornithine, and arginine (CYSQN / Cystinuria Profile, Quantitative, 24 Hour, Urine or CYSR / Cystinuria Profile, Quantitative,
CYSQN 8376

Cystinuria Profile, Quantitative, 24 Hour, Urine

Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestines and kidneys. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7000. Cystinuria is an autosomal recessive disease, but some heterozygous carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically nondisease causing, urinary cystine excretion. Cystinuria is caused by variants in genes, SLC3A1 on chromosome 2p and SLC7A9 on chromosome 19q. Initially, the disease was classified into subtypes I, II, and III (type II and III are also referred as nontype-I) based on the amount of urinary cystine excreted in heterozygous parental specimens. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to variants in the SLC3A1 gene; type B, due to variants in the SLC7A9 gene; and type AB, due to 1 variant in each SLC3A1 and SLC7A9 gene.

Useful For: Diagnosis of cystinuria

Interpretation: Homozygotes or compound heterozygotes with cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) is also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for nontype I cystinuria can be distinguished by the pattern of urinary amino acids excretion: homozygous individuals secrete large amounts of cystine and all 3 dibasic amino acids, whereas heterozygous individuals secrete more lysine and cystine than arginine and ornithine.

Reference Values:
CYSTINE
3-15 years: 11-53 mcmol/24 hours
> or =16 years: 28-115 mcmol/24 hours
**LYSINE**  
3-15 years: 19-140 mcml/24 hours  
> or =16 years: 32-290 mcml/24 hours

**ORNITHINE**  
3-15 years: 3-16 mcml/24 hours  
> or =16 years: 5-70 mcml/24 hours

**ARGININE**  
3-15 years: 10-25 mcml/24 hours  
> or =16 years: 13-64 mcml/24 hours

**Conversion Formulas:**  
Result in mcml/24 hours x 0.24 = result in mg/24 hours  
Result in mg/24 hours x 4.17 = result in mcml/24 hours

**Clinical References:**  

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**CYSR 81067**  
**Cystinuria Profile, Quantitative, Random, Urine**

**Clinical Information:** Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestines and kidneys. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7000. Cystinuria is an autosomal recessive disease, but some heterozygous carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically nondisease causing, urinary cystine excretion. Cystinuria is caused by variants in genes, SLC3A1 on chromosome 2p and SLC7A9 on chromosome 19q. Initially, the disease was classified into subtypes I, II, and III (type II and III are also referred as nontype-I) based on the amount of urinary cystine excreted in heterozygous parental specimens. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to variants in the SLC3A1 gene; type B, due to variants in the SLC7A9 gene; and type AB, due to 1 variant in each SLC3A1 and SLC7A9 gene.

**Useful For:** Biochemical diagnosis and monitoring of cystinuria

**Interpretation:** Homozygotes or compound heterozygotes with cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) is also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for nontype I cystinuria can be distinguished by the pattern of urinary amino acids excretion: homozygous individuals secrete large amounts of cystine and all 3 dibasic amino acids, whereas heterozygous individuals secrete more lysine and cystine than arginine and ornithine.

**Reference Values:**

<table>
<thead>
<tr>
<th>Urine Amino Acid</th>
<th>Reference Values (nmol/mg creatinine)</th>
<th>Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; or =12 Months (n=36)</td>
<td>13-35 Months (n=45)</td>
</tr>
<tr>
<td>Arginine (Arg)</td>
<td>10-560</td>
<td>20-395</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Symbol</td>
<td>Min</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>Ornithine</td>
<td>Orn</td>
<td></td>
</tr>
<tr>
<td>Cystine</td>
<td>Cys</td>
<td>12-504</td>
</tr>
</tbody>
</table>

**Clinical References:**

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**METR1**

**Cytochrome b5 Reductase Enzyme Activity, Blood**

**Clinical Information:** Cytochrome b5 reductase (CYB5R), also called methemoglobin reductase, is the enzyme within the erythrocyte that maintains hemoglobin in the reduced (non-methemoglobin) state. A deficiency of CYB5R in erythrocytes is an autosomal recessive disorder resulting from variants in the CYB5R3 or the CYB5A genes. Persons who are heterozygous for CYB5R genetic variants have no clinical or laboratory abnormalities, are not cyanotic, and have normal methemoglobin concentrations in their blood. However, they hold an increased risk for more severely symptomatic acute episodes of methemoglobinemia with exposure to inducing agents. Persons who are homozygous for CYB5R genetic variants have normal arterial oxygen saturation but have varying quantities of methemoglobin in their blood, generally 15% to 20%, and are quite cyanotic. Paradoxically, homozygotes typically have normal blood counts; the condition only rarely causes polycythemia. The presence of methemoglobin shifts the hemoglobin-O2 dissociation curve to the right, so although the transport of oxygen is diminished, the delivery of oxygen to tissues is normal. Because of the chronicity, the homozygous condition is usually compensated and, therefore, quite benign, but it may cause concern to parents of affected children, be a cosmetic embarrassment to the children, and alarm the attending physician. The cyanosis may be treated with methylene blue.

**Useful For:** Evaluation of patients with cyanosis Confirming cases of suspected cytochrome b5 reductase (methemoglobin reductase) deficiency Functional studies in families with cytochrome b5 reductase deficiency

**Interpretation:** Cytochrome b5 reductase (methemoglobin reductase) activity in neonates (0-6 weeks) is normally 60% of the normal adult value. Adult values are attained by 2 to 3 months of age. Heterozygotes have results slightly lower than the reference range. Homozygotes demonstrate little to no cytochrome b5 reductase activity and increased levels of methemoglobin.

**Reference Values:**
> or =12 months of age: 7.8-13.1 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

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**CYOXS**

**Cytochrome Oxidase Stain (Bill Only)**

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

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.
Cytochrome P450 1A2 Genotype, Varies

Clinical Information: The cytochrome P450 (CYP) family is involved in the primary metabolism of many drugs. The CYPs are a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs. CYP1A2-mediated drug metabolism is highly variable. A number of variants have been identified in the CYP1A2 gene that results in increased, diminished, or abolished catalytic activity and substrate metabolism. The frequency of these variants varies by ethnicity. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the CYP1A2 genotype. Individuals who are poor metabolizers may require lower than usual doses to achieve optimal response, whereas individuals who are ultrarapid metabolizers may benefit from increased doses. CYP1A2 phenotype is predicted based upon the number of functional, partially functional, nonfunctional, and inducible alleles present in a sample. In the absence of clear guidance on dosing for various metabolizer phenotypes, patients with either rapid or poor metabolism also may benefit by switching to another comparable drug that is not primarily metabolized by CYP1A2 or by therapeutic drug monitoring where applicable. The following table outlines the relationship between the variations (star alleles) detected in this assay and the effect on the activity of the enzyme produced by that allele. CYP1A2 allele Nucleotide change (legacy nomenclature) cDNA nucleotide change (NM_000761.4) Effect on enzyme metabolism (a) *1 None (wild type) Normal (extensive) activity *1F -163C>A c.-9-154C>A Increased inducibility *1K -729C>T c.-10+113C>T Decreased activity and decreased inducibility *6 5090C>T c.1291C>T No activity *7 3533G>A c.1253+1G>A No activity a. Effect of a specific allele on the activity of the CYP1A2 enzyme can only be estimated since the literature does not provide precise data. (1-5) A complicating factor in correlating CYP1A2 genotype to CYP1A2 phenotype is that some drugs or their metabolites are inhibitors of CYP1A2 catalytic activity. These drugs may reduce CYP1A2 catalytic activity. Consequently, an individual may require a dose decrease greater than predicted based upon genotype alone. Another complicating factor is that CYP1A2 is inducible by several drugs and environmental agents (eg, cigarette smoke) and the degree of inducibility is under genetic control. It is important to interpret the results of testing in the context of other coadministered drugs and environmental factors.

Useful For: Identifying individuals who are poor, intermediate, normal (extensive) or rapid metabolizers of drugs metabolized by cytochrome P450 1A2 to assist drug therapy decision making

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium. (6) CYP1A2 activity is also dependent upon hepatic function status, as well as age. Renal function may be important for drugs that are excreted in urine. Patients may develop drug toxicity if hepatic or renal function is decreased. Drug metabolism is known to decrease with age. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and age. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values: An interpretive report will be provided.

Cytochrome P450 2B6 Genotype, Varies

Clinical Information: The cytochrome P450 (CYP) family of enzymes is a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. CYP2B6 is wholly or partially responsible for the metabolism of several commonly prescribed drugs. The CYP2B6 gene is highly variable with over 38 named alleles. The gene can have multiple sequence variations. Alleles thought to have an impact upon CYP2B6 enzyme function at the time that this test was developed are included in this test (See Table 1). Individuals without a detectable gene alteration will be reported as CYP2B6*1/*1, but it is possible that these individuals harbor unknown variants that may impact metabolism. In addition, some individuals have genes that are hybrids of CYP2B6 and the CYP2B7 pseudogene. The frequency of these hybrids is unknown, and this assay does not test for these hybrids. Phenotyping is derived from the Pharmacogene Variation Consortium website(1), an exhaustive review of the CYP2B6 literature, the Clinical Pharmacogenetics Implementation Consortium website(2), and published guidelines.(3) CYP2B6 genotype results are used to predict metabolizer phenotypes. A CYP2B6 phenotype is predicted based upon the number of functional, partially functional, and nonfunctional alleles present in a sample. In rare instances where alleles with unknown function are present in a homozygous or compound heterozygous state, an unknown phenotype occurs. It should be noted that other laboratories may use different phenotype prediction methods as there is no consensus on this at this time. However, the method used here represents the findings of the majority of literature available. Several medications act as substrates of CYP2B6. CYP2B6-metabolized medications with the highest quality of data for the impact of various CYP2B6 alleles on metabolism are: -Bupropion -Efavirenz -Ketamine -Methadone -Nevirapine Other enzymes may be involved in the metabolism of these drugs. For example, bupropion is also metabolized by CYP2D6. Efavirenz is also metabolized by CYP2A6, although CYP2B6 is the major metabolizing enzyme. Ketamine is also metabolized by CYP2A6, and nevirapine is also metabolized by CYP3A4 and CYP3A5. CYP2A6 testing is not available clinically at the time this document was written, but CYP2D6 (2D6Q / Cytochrome P450 2D6 Comprehensive Cascade, Varies), CYP3A4 (3A4Q / Cytochrome P450 3A4 Genotype, Varies), and CYP3A5 (3A5Q / Cytochrome P450 CYP3A5 Genotype, Varies) testing is available. There is a variable degree of substrate specificity exhibited by CYP2B6 alleles on these medications. This means that the same allele (ie, *6) may not metabolize all substrates at exactly the same rate. Drugs that are metabolized by CYP2B6 may require dosage adjustment based on the individual patient's genotype. For example, patients who are poor metabolizers may require much lower than usual doses to achieve optimal response in the case of drugs that are inactivated by the CYP2B6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that are inactivated by CYP2B6 enzyme. In the absence of clear guidance from the FDA on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit by switching to comparable alternate medications that are not primarily metabolized by CYP2B6 or by therapeutic drug monitoring where applicable. Table 1. Enzyme Activity of Individual Star Alleles

<table>
<thead>
<tr>
<th>Enzyme Activity</th>
<th>Normal (extensive) activity</th>
<th>Decreased activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*8, *12, *13</td>
<td>*16 (also known as *18.002)</td>
<td>*18, *35, *38</td>
</tr>
</tbody>
</table>

Useful For: Aiding in determining therapeutic strategies for drugs that are metabolized by cytochrome P450 (CYP) 2B6 Providing information relevant to bupropion, efavirenz, ketamine, methadone, and nevirapine, as well as other medications metabolized by CYP2B6 Determining the genotype if genotype-phenotype discord is encountered clinically after testing with a less comprehensive genotyping method has occurred Identifying genotype when required for drug trials and research protocols

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.
Clinical Information: Primary metabolism of many drugs is performed by the cytochrome P450 (CYP) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C19, participates in the metabolism of a wide variety of drugs, including the activation of the anticoagulant clopidogrel and the inactivation of citalopram. CYP2C19 drug metabolism is variable among individuals. Some individuals have CYP2C19 genetic variants that lead to severely diminished or absent CYP2C19 catalytic activity (ie, poor metabolizers). The frequency of CYP2C19 variants (also referred to as polymorphisms) depends on ethnicity. CYP2C19 variants that produce poor metabolizers are found with frequencies of 2% to 5% in the white population, 4% in African Americans, 13% to 23% in Asians, and 38% to 79% in Polynesians and Micronesians. The following table displays the CYP2C19 variants detected by this assay, the corresponding star allele, and the effect on CYP2C19 enzyme activity: 

<table>
<thead>
<tr>
<th>CYP2C19a allele</th>
<th>cDNA nucleotide change (NM_000769.1)</th>
<th>Effect on enzyme activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Normal (extensive) activity</td>
<td>Normal (extensive) activity</td>
</tr>
<tr>
<td>*2</td>
<td>c.681G&gt;A</td>
<td>No activity</td>
</tr>
<tr>
<td>*3</td>
<td>c.636G&gt;A</td>
<td>No activity</td>
</tr>
<tr>
<td>*4</td>
<td>c.1A&gt;G</td>
<td>No activity</td>
</tr>
<tr>
<td>*5</td>
<td>c.1297C&gt;T</td>
<td>Decreased activity</td>
</tr>
<tr>
<td>*6</td>
<td>c.395G&gt;A</td>
<td>Decreased activity</td>
</tr>
<tr>
<td>*7</td>
<td>c.819+2T&gt;A</td>
<td>Decreased activity</td>
</tr>
<tr>
<td>*8</td>
<td>c.358T&gt;C</td>
<td>Decreased activity</td>
</tr>
<tr>
<td>*9</td>
<td>c.431G&gt;A</td>
<td>Enhanced activity</td>
</tr>
<tr>
<td>*10</td>
<td>c.680C&gt;T</td>
<td>Enhanced activity</td>
</tr>
<tr>
<td>*17</td>
<td>c.-806C&gt;T</td>
<td>Enhanced activity</td>
</tr>
<tr>
<td>*35</td>
<td>c.332-23A&gt;G</td>
<td>No activity</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Phenotyping is derived from the Pharmacogene Variation Consortium website(1), the Clinical Pharmacogenetics Implementation Consortium website(2), published guidelines(3-8), and an exhaustive review of the CYP2C19 literature(9-10). Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19*1/*1. If an individual is homozygous or compound heterozygous for alleles with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. Individuals with the CYP2C19*17 allele (in the absence of any inactive or decreased activity alleles) may have enhanced metabolism of drugs. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C19. It is important to interpret the results of testing in the context of other coadministered drugs.

Useful For: Identifying patients who may be at risk for altered metabolism of drugs that are modified by cytochrome P450 2C19 Predicting anticoagulation response to clopidogrel

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered when treating intermediate metabolizers. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values: An interpretive report will be provided.

An interpretive report will be provided.


Cytochrome P450 2C9 Genotype, Varies

Clinical Information: Primary metabolism of many drugs is performed by the cytochrome P450 (CYP) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues, but primarily in the intestines and liver. One of these CYP450 enzymes, CYP2C9, participates in the metabolism of a wide variety of drugs including warfarin and phenytoin. CYP2C9-mediated drug metabolism is variable among individuals. Some individuals have CYP2C9 genetic variants that lead to severely diminished or absent CYP2C9 catalytic activity (ie, poor metabolizers). These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. A number of specific CYP2C9 variants have been identified that result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in the assay and their effect on enzyme activity: CYP2C9 allele cDNA nucleotide change (NM_000771.3) Effect on enzyme metabolism *1 None (wild type) Normal activity *2 c.430C>T Reduced activity *3 c.1075A>C No activity *4 c.1076T>C Reduced activity *5 c.1080C>G Reduced activity *6 c.818delA No activity *8 c.449G>A Reduced activity *9 c.752A>G Normal activity *11 c.1003C>T Reduced activity *12 c.1465C>T Reduced activity *13 c.269C>T No activity *14 c.374G>A Reduced activity *15 c.485C>A No activity *16 c.895A>G Reduced activity *17 c.1144C>T Reduced activity *18 c.1190A>C No activity *25 c.353_362del No activity *26 c.389C>G Reduced activity *28 c.641A>T Reduced activity *30 c.1429G>A Reduced activity *33 c.395G>A No activity *35 c.374G>T;430C>T No activity CYP2C9 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. Phenotyping is derived from the Pharmacogene Variation Consortium website(1), the Clinical Pharmacogenetics Implementation Consortium website (2), published guidelines (3-5), and an exhaustive review of the CYP2C9 literature (6-7). Individuals without a detectable CYP2C9 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C9 *1/*1. If an individual is homozygous or compound heterozygous for an allele with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C9. It is important to interpret the results of testing in the context of other coadministered drugs.
Useful For: Identifying individuals who may be at risk for altered metabolism of drugs that are modified by cytochrome P450 2C9

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium. (1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug/metabolite inhibition must be considered in the case of all metabolizer categories except poor metabolizer. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.


Cytochrome P450 2D6 Comprehensive Cascade, Varies

Clinical Information: The cytochrome P450 (CYP) family of enzymes is a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of the CYP enzymes, CYP2D6, is wholly or partially responsible for the metabolism of many commonly prescribed drugs. The CYP2D6 gene is highly variable with over 100 named alleles. The gene may be deleted, duplicated, and multiplied, and can have multiple sequence variations. In addition, some individuals have genes that are hybrids of CYP2D6 and the CYP2D7 pseudogene. Some individuals have CYP2D6 variants that result in synthesis of an enzyme with decreased or absent catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly. CYP2D6 duplications and multiplications involving active alleles may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict metabolizer phenotypes. (See Table 1) Table 1. Enzyme Activity of Individual Star Alleles Enzyme activity Examples of CYP2D6 star alleles Normal (extensive) metabolism *1, *2, *2A, *35 Decreased activity *9, *10, *14, *17, *29, and *41 No or null activity *3, *4, *4N, *5, *6, *7, *8, *11, *12, *13, *15, *36, *68, *114 CYP2D6 phenotype is predicted based upon the number of functional, partially functional, and nonfunctional alleles present in a sample. Phenotyping is derived from the Pharmacogene Variation Consortium website (1), the Clinical Pharmacogenetics Implementation Consortium website (2), published guidelines (3-8), and an exhaustive review of the CYP2D6 literature (9-10). There are instances where a precise phenotype prediction is not possible, and in these instances, a range of possible phenotypes will be given. Individuals without a detectable gene alteration will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2D6*1/*1. Drugs that are metabolized through CYP2D6 may require dosage adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response in the case of drugs that are inactivated by the CYP2D6 enzyme and higher than usual doses in
the case of drugs that are activated by CYP2D6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that are inactivated by CYP2D6 enzyme and lower doses in the case of drugs that are activated by CYP2D6. In the absence of clear guidance from FDA on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit by switching to comparable alternate medications not primarily metabolized by CYP2D6 or by therapeutic drug monitoring where applicable. Overall, this test provides a comprehensive CYP2D6 genotype result for patients, ensuring a more accurate phenotype prediction. This assay has clinical significance for patients taking or considering medications activated (eg, codeine, tramadol, and tamoxifen) or inactivated (eg, antidepressants and antipsychotics) by the CYP2D6 enzyme. Sequential tier testing associated with this test will be initiated until the least ambiguous phenotype possible is determined.

**Useful For:** Providing information relevant to tamoxifen, codeine, and tramadol, as well as other medications metabolized by cytochrome P450 2D6 Determining the exact genotype when other methods fail to generate this information or if genotype-phenotype discord is encountered clinically Identifying precise genotype when required (eg, drug trials, research protocols) Identifying novel variants that may interfere with drug metabolism (when reflex to sequencing is performed)

**Interpretation:** A comprehensive interpretive report will be provided, which combines the results of all tier testing utilized to obtain the final genotype. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For the CYP2D6 copy number variation assay, the reportable copy number range is 0 to 4 copies for each of the CYP2D6 region assessed. Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
A comprehensive interpretive report will be provided.

Clinical Information: CYP3A4 is a member of the CYP3A family of genes located on chromosome 7. The cytochrome P450 (CYP) 3A subfamily of enzymes is responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells, including some lipid-lowering drugs. The CYP3A4 enzyme activity is highly variable. Interindividual differences in enzyme expression may be due to several factors including: variable homeostatic control mechanisms, disease states that alter homeostasis, up- or down-regulation by environmental stimuli, and genetic variation.(1) One variant, CYP3A4*22 (c.522-191C>T), has been studied extensively. This variant affects hepatic expression of CYP3A4 and response to statin drugs. The CYP3A4*22 allele is associated with reduced CYP3A4 activity, which may result in a better response to lipid-lowering drugs, such as simvastatin, atorvastatin, or lovastatin. However, reduced CYP3A4 activity may also be associated with statin-induced myopathy, especially for simvastatin. Studies show that in livers with the reference (wild-type) genotype (homozygous C or CC) the CYP3A4 mRNA level and enzyme activity were 1.7- and 2.5-fold greater than in CYP3A4*22 heterozygotes (CT) and homozygotes (TT), respectively. In 235 patients taking stable doses of drugs for lipid control, carriers of the T allele required significantly lower statin doses for optimal lipid control than did non-T carriers.(2) These results indicate that CYP3A4*22 markedly affects expression of CYP3A4 and could serve as a biomarker for CYP3A4 metabolizer phenotype. The reported allele frequency of CYP3A4*22 is 5% to 8% in the white population and 4.3% in African American and Chinese populations. Other alleles have not been as extensively studied in clinical trials but are expected to have similar impacts on statin metabolism and the metabolism of other drugs primarily metabolized by CYP3A4. The following table displays the CYP3A4 variants detected by this assay, the corresponding star allele, and the effect on CYP3A4 enzyme activity. Individuals without a detectable CYP3A4 variant are designated as CYP3A4*1/*1. CYP3A4 allele cDNA nucleotide change (NM_017460.5) Effect on enzyme activity *1 None (wild type) Normal activity *8 c.389G>A No activity *11 c.1088C>T Reduced activity *12 c.1117C>T Reduced activity *13 c.1247C>T No activity *16 c.554C>G Minimal activity *17 c.566T>C No activity *18 c.878T>C Reduced activity *22 c.522-191C>T Reduced activity *26 c.802C>T No activity Genotype to phenotype predictions are based on the Pharmacogene Variation Consortium website (3) and review of the CYP3A4 literature.

Useful For: Aids in determining therapeutic strategies for drugs that are metabolized by cytochrome P450 3A4, including atorvastatin, simvastatin, and lovastatin. This test is not useful for managing patients receiving fluvasatin, rosuvastatin, or pravastatin since these drugs are not metabolized appreciably by CYP3A4.

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(3) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values: An interpretive report will be provided.

Clinical Information: CYP3A5 is a member of the CYP3A family of genes located on chromosome 7. The cytochrome P450 (CYP) 3A subfamily of enzymes responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells. The CYP3A5 expression level and enzymatic activity can be modulated by genetic variation. CYP3A5 allelic frequency depends upon ethnicity. For example, in individuals of European descent the most common allele is the CYP3A5*3 allele (c.219-237A>G), which results in a splicing defect and absence of enzyme activity. In individuals of African descent, the *1 allele (functional enzyme) is most common. The distribution of CYP3A5*3 allele frequencies ranges from 0.14 among sub-Saharan Africans to 0.95 in European populations. CYP3A5 testing is commonly ordered for patients receiving tacrolimus. Tacrolimus is an immunosuppressive calcineurin inhibitor used in transplant recipients. Tacrolimus has a low therapeutic index with a wide range of side effects and large interindividual variability in its pharmacokinetics, particularly in the dose required to reach target trough blood concentrations, thus necessitating routine therapeutic drug monitoring in clinical practice. Tacrolimus dose requirements are most closely associated with CYP3A5 genotype even though the drug is metabolized by both CYP3A4 and CYP3A5. According to existing literature and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, individuals with at least one copy of fully functional CYP3A5 (ie, *1/*1 and *1/*3) require a higher dose of tacrolimus to reach the targeted whole blood concentrations than those without a copy of a fully functional CYP3A5 allele (ie, *3/*3) (2-5). CYP3A5 genotyping may predict dose requirements for tacrolimus but does not replace the need for therapeutic monitoring to guide tacrolimus dose adjustments. For a patient with the CYP3A5*3/*3 genotype, initiating tacrolimus therapy with a standard (normal) dose is recommended. One of the complications in interpreting CYP3A5 genotyping results and the effect of genotype on drug dosing is the fact that most individuals involved in drug trials have been of European descent. Individuals of European decent are more likely to have the CYP3A5*3/*3 genotype, which predicts a poor metabolizer phenotype. Dosing requirements were derived from these clinical trials so individuals with 1 or 2 copies of CYP3A5*1, will functionally behave as though they have increased activity and may require higher doses of CYP3A5 metabolized drugs. The following table displays the CYP3A5 variants detected by this assay, the corresponding star allele, and the effect on CYP3A5 enzyme activity: CYP3A5 allele cDNA nucleotide change (NM_000777.4) Effect on enzyme activity

<table>
<thead>
<tr>
<th>CYP3A5 Allele</th>
<th>Effect on CYP3A5 Enzyme Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 (None/wild type)</td>
<td>Normal activity</td>
</tr>
<tr>
<td>*3 (c.219-237A&gt;G)</td>
<td>No activity</td>
</tr>
<tr>
<td>*5 (c.432+2T&gt;C)</td>
<td>No activity</td>
</tr>
<tr>
<td>*6 (c.624G&gt;A)</td>
<td>No activity</td>
</tr>
<tr>
<td>*7 (c.1035dup)</td>
<td>No activity</td>
</tr>
<tr>
<td>*8 (c.82C&gt;T)</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>*9 (c.1009G&gt;A)</td>
<td>Reduced activity</td>
</tr>
</tbody>
</table>

Useful For: Aids in optimizing treatment with tacrolimus and other drugs metabolized by cytochrome P450 3A5

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by Pharmacogene Variation (PharmVar) Consortium. (1) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values: An interpretive report will be provided.

Cytokine Panel 13

**Interpretation:** Results are used to understand the pathophysiology of immune, infectious, or inflammatory disorders, or may be used for research purposes.

**Reference Values:**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Necrosis Factor-alpha</td>
<td>7.2 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 2</td>
<td>2.1 pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 2 Receptor Soluble</td>
<td>175.3 pg/mL to 858.2 pg/mL</td>
</tr>
<tr>
<td>Interleukin 12</td>
<td>1.9 pg/mL or less</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>4.2 pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 4</td>
<td>2.2 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 5</td>
<td>2.1 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 10</td>
<td>2.8 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 13</td>
<td>2.3 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 17</td>
<td>1.4 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 1 beta</td>
<td>6.7 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>2.0 Å pg/mL or less</td>
</tr>
<tr>
<td>Interleukin 8</td>
<td>3.0 Å pg/mL or less</td>
</tr>
</tbody>
</table>

Cytokine Panel, Plasma

**Clinical Information:** Cytokines are important mediators of cell-to-cell communication within the innate and adaptive immune systems. The expression of most cytokines is highly regulated and generally occurs in response to foreign or self-antigenic stimulation. The functions of cytokines are extremely varied, with many cytokines also displaying pleiotropic effects, depending on their cellular target. Some cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 beta, IL-6, interferon (IFN)-alpha and beta, IL-10, and IL-18 are particularly important in the innate immune response. For example, TNF, IL-1 beta, and IL-6 induce expression of acute phase proteins in the liver. TNF and IL-1 beta also lead to endothelial activation and are critical regulators of the hypothalamus, which can result in elevated body temperature. IL-6, in comparison, is a bridge to the adaptive immune response, by acting on B cells to induce proliferation. In contrast, IFN-alpha and IFN-beta (members of the type I IFN family) are key components of the innate immune response to viral infections. IFN-gamma, which is a type II IFN, has roles in both the innate and adaptive immune responses, including macrophage activation, induction of B-cell isotype switching, and T helper type 1 cell differentiation. Other cytokines, such as monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha (MIP-1alpha), are categorized as chemokines because they function primarily to attract leukocytes to the site of inflammation. Further, some cytokines act on hematopoietic stem cells to induce differentiation of various leukocytes. For example, granulocyte-monocyte colony stimulating factor (GM-CSF) induces myeloid progenitor cells to differentiate into neutrophils and monocytes. Lastly, for some cytokines, soluble forms of the receptor can be found in the peripheral circulation. The IL-2 soluble receptor is produced from proteolytic cleavage of the membrane-bound receptor, which occurs during T-cell activation. As a group, cytokines and their receptors represent a highly complex and critical regulator of a normal immune response.

**Useful For:** Understanding the etiology of infectious or chronic inflammatory diseases, when used in conjunction with clinical information and other laboratory testing. Research studies in which an assessment of cytokine responses is needed.
**Interpretation:** Elevated cytokine concentrations could be consistent with the presence of infection or other inflammatory process.

**Reference Values:**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Normal value (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>IFN-beta</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>&lt; or =198</td>
</tr>
<tr>
<td>IL-1 beta</td>
<td></td>
</tr>
<tr>
<td>IFN-gamma</td>
<td></td>
</tr>
<tr>
<td>MIP-1 alpha</td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td></td>
</tr>
<tr>
<td>IL-2 receptor alpha soluble</td>
<td>&lt; or =959</td>
</tr>
<tr>
<td>IFN-alpha</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td>&lt; or =468</td>
</tr>
</tbody>
</table>

**Clinical References:**

**CFNPC 113344**
Cytology FNA (Bill Only)
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**CTPPC 113340**
Cytology Touch Prep (Bill Only)
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**CTAPC 113341**
Cytology Touch Prep Additional (Bill Only)
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
Cytomegalovirus (CMV) Antibodies, IgG, Serum

**Clinical Information:** Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow-derived cells. (1) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. (2,3) Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in children between the ages of 6 to 11 and adults over 80 years old, respectively. (4)

**Useful For:** Determining whether a patient (especially transplant recipients, organ and blood donors) has had a recent infection or previous exposure to cytomegalovirus.

**Interpretation:** Positive cytomegalovirus (CMV) IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are, therefore, considered susceptible to primary infection.

**Reference Values:**
Negative (reported as positive, negative, or equivocal)

**Clinical References:**

Cytomegalovirus (CMV) Antibodies, IgM and IgG, Serum

**Clinical Information:** Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. Primary CMV infection in immunocompetent individuals may manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in children between 6 to 11 years of age and adults over 80 years old, respectively.

**Useful For:** Aiding in the diagnosis of acute or past infection with cytomegalovirus (CMV)
Determination of prior exposure to CMV This test should not be used for screening blood or plasma donors.
**Interpretation:** IgM: A negative cytomegalovirus (CMV) IgM result suggests that the patient is not experiencing acute or active infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection where the time of seroconversion is not well defined as high as 28% (10/36) of pregnant women did not demonstrate CMV IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary rather than primary infections. IgG: Positive CMV IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are, therefore, considered susceptible to primary infection. Equivocal CMV IgM or IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated.

**Reference Values:**

**CYTOMEGALOVIRUS IgM:**

- Negative

**CYTOMEGALOVIRUS IgG:**

- Negative

Reference values apply to all ages.

**Clinical References:**


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**Cytomegalovirus (CMV) Antibodies, IgM, Serum**

**Clinical Information:** Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow-derived cells. Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is 1 of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States, the prevalence of CMV specific antibodies increases from approximately 36% to over 91% in children between the ages of 6 to 11 and adults over 80 years old, respectively.

**Useful For:** Aiding in the diagnosis of acute infection with cytomegalovirus. This test should not be used for screening blood or plasma donors.

**Interpretation:** A negative cytomegalovirus (CMV) IgM result suggests that the patient is not experiencing acute or active infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM
responses within 8 weeks postinfection. In cases of primary infection where the time of seroconversion is not well defined as high as 28% (10/36) of pregnant women did not demonstrate CMV-IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary, rather than primary, infections. Equivocal CMV IgM results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated.

Reference Values:
Negative
Reference values apply to all ages.


Cytomegalovirus (CMV) CD8 T-Cell Immune Competence, Quantitative Assessment by Flow Cytometry, Blood

Clinical Information: Cytomegalovirus (CMV), a double-stranded DNA virus, belongs to the Herpesviridae family of viruses and is structurally similar to other herpes viruses. Although many human strains of CMV exist, there is little genetic homology between human CMV and CMV of other species. The reported seroprevalence rates of CMV range from 40% to 100% in the general population. In the urban United States, the seroprevalence of CMV has been reported to be 60% to 70%.(1) However, data from Mayo Clinic's laboratory indicate that the seroprevalence in the Midwestern US population is closer to 30% (unpublished observations). Once CMV infection occurs, the virus spreads hematogenously to almost every organ. After acute infection, the virus enters a latent phase. Activation from this phase can be seen after acute illness, immunosuppression in allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation, or use of chemotherapy agents. CMV infection or reactivation has been implicated in allograft rejection in renal(2) and cardiac transplantation.(1) In cardiac transplants, CMV infection has been shown to contribute to accelerated development of transplant atherosclerosis (cardiac allograft vasculopathy). CMV remains a significant cause of morbidity and mortality after HSCT. Of allogeneic HSCT patients who are CMV-seropositive, 60% to 70% will experience reactivation and, without ganciclovir or other preemptive therapy, 20% to 30% will develop end-organ disease.(3) CD8 T cells play a critical role in viral immunity, and CD8 T-cell effector functions include cytotoxicity and cytokine production. Cytotoxicity occurs after CD8 T-cell activation, causing target cell apoptosis. Cytotoxic T-cell responses mediate killing of target cells via 2 major pathways, granule-dependent (perforin and granzymes) and granule-independent (Fas and Fas ligand (FasL)) mechanisms. The granule-dependent pathway does not require the de novo synthesis of proteins by effector CD8 T cells, but rather it utilizes preformed lytic granules located within the cytoplasm. Among the proteins in these preformed lytic granules are the lysosomal-associated membrane proteins (LAMP), including LAMP-1 (CD107a) and LAMP-2 (CD107b). These proteins are not normally found on the surface of T cells. Degranulation of activated CD8 T cells occurs rapidly after T-cell receptor (TCR) stimulation, exposing CD107a and CD107b. The cytokines produced by activated T cells include interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), macrophage inflammatory protein 1 alpha (MIP-1 alpha), macrophage inflammatory protein 1 beta (MIP-1 beta), and interleukin-2 (IL-2). Several studies have shown the importance of cytotoxic T-cell responses to CMV in conferring protection from subsequent CMV disease. Antiviral drugs have helped reduce the incidence of early CMV infection, and acyclovir and ganciclovir have been the mainstay of antiviral treatment for a number of years, although these drugs have poor bioavailability.(4)
development of the new antiviral drugs valacyclovir and valganciclovir (by the addition of a valine ester) has increased the bioavailability of these drugs by 10-fold.(4) There is some data to suggest valganciclovir prophylaxis may be considered for HSCT patients who are at high risk for infection and disease, though there is a need for further study in this area.(5) Two main strategies have been used for the prevention of early CMV infection and disease in CMV-seropositive patients and in seronegative recipients who receive a seropositive graft-preemptive therapy: -Patient monitoring for CMV infection and treatment only when CMV viremia is present. -Prophylactic management-where all patients receive treatment after transplantation with the goal of preventing CMV disease.(5) The disadvantage of prophylactic therapy is that it requires monitoring for myelosuppression and infections-side effects of antiviral drug therapy. Despite this disadvantage, there are several reasons to consider prophylaxis, including the fact that the incidence of recurrent infections after treatment is 30% to 40%,(5) patients receiving preemptive therapy have a 5% CMV disease break-through, and prophylaxis reduces the risk of viral reactivation. Late CMV infection occurs 3 months after transplantation and is now recognized as a significant cause of morbidity after allogeneic HSCT. These complications usually occur in the setting of continued immunosuppression for chronic graft-versus-host disease (GVHD). The clinical manifestations of late CMV disease differ slightly from those seen early after transplantation. Within the first 100 days after HSCT, almost all patients with CMV disease have CMV pneumonia or gastrointestinal disease. In late CMV disease, the more unusual manifestations of CMV infection (eg, CMV retinitis, CMV-associated bone marrow failure, or CMV encephalitis) tend to occur.(6) These late manifestations occur in a setting of continued CMV-specific T-cell immunodeficiency. Therefore, it is necessary to monitor CMV-specific CD8 T-cell responses, in addition to viral load, to effectively identify patients at higher risk of CMV disease. It has been shown that ganciclovir may delay the recovery of the protective CMV-specific T-cell response, which may contribute to the occurrence of late CMV disease.(7) The use of ganciclovir as early treatment after detection of CMV in blood or other body fluid and as a prophylaxis for CMV infection in bone marrow transplant (BMT) and heart transplant recipients has dramatically reduced the incidence of CMV in these immunocompromised hosts. Yet, early treatment and prophylaxis have not been uniformly successful, with up to 15% of BMT recipients developing CMV disease after discontinuation of antiviral therapy. Similarly, patients undergoing lung transplantation have been shown to be only transiently protected with antiviral agents. These data suggest that the CMV-specific responses necessary for protection may not recover during the time the host is receiving antiviral therapy. Ganciclovir exerts its antiviral effects at the stage of viral DNA replication and, therefore, in the presence of the drug, infected cells may express some of the immediate early and early gene products, but not the full complement of CMV genes required for replication and virion formation. In latently infected CMV-seropositive individuals, the HLA class I-restricted cytotoxic T lymphocyte response to CMV is predominantly specific for epitopes derived from structural virion proteins. Therefore, in patients receiving ganciclovir, the viral antigens may be inadequate to activate host T-cell responses, resulting in the failure to reconstitute CMV-specific immunity. In fact, a prospective, randomized placebo-controlled study of ganciclovir prophylaxis revealed that when ganciclovir therapy is discontinued, a larger fraction of patients (who received the drug) are deficient in CMV-specific T-cell immunity at day 100 than in the placebo group.(7) That study also showed that bone marrow donor serology has an important influence on the early detection of virus-specific T-cell responses.(7) Not all medical centers use ganciclovir for prophylaxis; some use acyclovir and the same findings may apply in this case as well. In a more recent study, it was shown that impaired CD8 function was associated with the use of high-dose steroids, bone marrow as a source of stem cells, and CD8 T-cell lymphopenia.(3) In the absence of high-dose steroids, low-level subclinical CMV antigenemia was found to stimulate both CD4 and CD8 functional recovery in recipients of ganciclovir prophylaxis, suggesting that subclinical CMV reactivation while on antiviral therapy can be a potent stimulator of T-cell function.(3) Regardless of antiviral therapy, immunologic reconstitution remains the key element in protection from late-onset CMV disease. This test assesses the number of CMV-specific CD8 T cells and their function (activation via production of the cytokine IFN-gamma and cytotoxic potential via CD107a and CD107b as markers of degranulation) using a panel of 5 major histocompatibility complex (MHC) class I alleles (HLA A1, A2, B7, B8, and B35) along with their respective immunodominant CMV epitopes. This 3-part assay allows a comprehensive assessment of CMV-specific CD8 T-cell immunity and, when combined with evaluation of viremia using molecular analyses, provides a more accurate picture of the nature of CMV reactivation and the corresponding immune response than evaluating viremia alone. Assessment of Global CD8 T-Cell Function: CD8 T cell activation occurs either through the TCR-peptide-MHC or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen
nonspecific. Impairment of global CD8 T cell activation (due to inherent cellular immunodeficiency or as a consequence over immunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimitabolites (eg, mycophenolate mofetil), and thymoglobulin. The incorporation of global CD8 T cell function in this assay is helpful in determining if the lack of CMV-specific (antigen-specific) response is due to a global impairment in CD8 T cell function, due to immunosuppression or other causes, or whether the lack of CMV CD8 T cell immunity is unrelated to overall CD8 T cell function. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(8) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(9-11) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(9) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening (12), and during summer compared to winter.(13) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Assessing cytomegalovirus (CMV)-specific immune competence in allo-hematopoietic stem cell transplantation patients who are at risk for developing late CMV disease (beyond day 100 after transplant) Assessing CMV-specific immune competence in solid organ transplant patients who are at high risk for CMV reactivation posttransplant Monitoring immune competence in patients post-primary CMV infection after transplant who are at risk for CMV reactivation after the cessation of antiviral prophylaxis Identifying individuals who are likely to be protected from posttransplant CMV infection and those who are at higher risk of CMV reactivation The global CD8 T cell immune competence assay is useful for determining over immunosuppression within the CD8 T cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** For allogeneic hematopoietic stem cell transplantation (HSCT) and solid organ transplant patients who are cytomegalovirus (CMV)-seropositive and at risk for CMV reactivation, posttransplant results should be compared to pretransplant (preconditioning/baseline) results. The report includes absolute CD3 and CD8 T-cell counts as well as a derived CMV-specific CD8 T-cell count (derived from CD3 and CD8 T-cell counts). The absolute count of CMV-CD8 T cells that are activated and have cytotoxic function in response to specific CMV peptide is also provided. The data from the 3 components of this assay should be interpreted together and not individually. In the setting of CMV viremia, frequent monitoring of CMV-immune competence helps define the evolution of the CMV-immune response. In this clinical context, CMV-immune competence should be measured as frequently as viral load to determine correlation between the 2 parameters. CMV-specific CD8 T-cell counts may show a decline in numbers over time in the absence of active infection or antigenemia. The absence of CMV-specific CD8 T cells may be a risk factor in the immune-compromised or immune-incompetent transplant patient, who is at risk for CMV reactivation. The presence of CMV-specific CD8 T cells may not be protective in itself. If the CMV-specific CD8 T cells do not show appropriate cytotoxic function (due to the fact that they recognize CMV epitopes that do not effectively induce a cytotoxic response), these patients may be at higher risk of an inadequate immune response to CMV infection. While the reference values provide a guideline of CMV-specific CD8 T-cell numbers and function in a cohort of healthy individuals, baseline (pretransplant/preconditioning) assessments should be taken into consideration when determining CMV-specific immune competence posttransplant. Correlation between data from multiple post-transplant specimens (if available) and the presence or absence of viremia (or active CMV disease) also are useful in the interpretation of results. CD8 T cell counts are elevated when the immune system is initially reconstituted post-HSCT, and the CD4 to CD8 ratio can be inverted for about 12 months post-HSCT. Interferon-gamma (IFN-gamma) and CD107a/b expression below the defined reference range are consistent with a global impairment in CD8 T cell function, most likely due to over-immunosuppression. IFN-gamma and CD107a/b levels greater than the defined reference range are unlikely to have any clinical significance.
Reference Values:
Total CD3 T cells: 884-5,830 x 10^3/mL
Total CD8 T cells: 168-1,847 x 10^3/mL
Total CMV CD8 T cells: 0-115 x 10^3/mL

The adult reference values were determined for healthy adult controls ages 20 to 80 years (n=94), for HLA A1, A2, B7, B8, and B35 alleles.

Reference values for CMV-specific T cells that are functional (interferon-gamma+, IFN-g+) and have cytotoxic activity (CD107a and CD107b expression, CD107a/b+):
Total CMV CD8 T-cells IFN-g: 0.028-52.200 x 10^3/mL
Total CMV CD8 T-cells CD107a/b: 0.252-50.760 x 10^3/mL

The 95% confidence interval reference values were determined from 102 healthy adult donors:
Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%
CD107a/b expression (as % CD8 T cells): 8.5-49.1%

The reference values were developed for each of the following 4 major histocompatibility complex class I alleles: A1, A2, B7, and B8 (n=45). We were unable to develop ranges for the B35 allele due to a lack of matching donors. The data is expressed as the absolute number of CMV-specific CD8 T cells that are IFN-gamma+ or CD107a/b+.

Clinical References:

Cytomegalovirus (CMV) DNA Detection and Quantification by Real-Time PCR, Plasma

Clinical Information: Cytomegalovirus (CMV) is a common and major cause of opportunistic infection in organ transplant recipients, causing significant morbidity and mortality. CMV infection and disease typically occur during the first year after organ transplantation after cessation of antiviral prophylaxis. Such infection usually manifests as fever, leukopenia, hepatitis, colitis, or retinitis. Other manifestations of CMV infection in this population may be more subtle and include allograft injury and loss, increased susceptibility to infections with other organisms, and decreased patient survival (ie, indirect effects). The risk of CMV disease is highest among organ recipients who are CMV seronegative
prior to transplantation and receive allografts from CMV-seropositive donors (ie, CMV D+/R- mismatch). The infection is transmitted via latent CMV present in the transplanted organ donor and the virus subsequently reactivates, causing a primary CMV infection in the recipient. CMV disease may also occur from reactivation of the virus already present within the recipients. Factors, such as the type of organ transplanted, intensity of the antirejection immunosuppressive therapy, advanced age, and presence of comorbidities in the recipient, are also associated with increased risk for CMV disease after allograft transplantation. Lung, heart, small intestine, pancreas, and kidney-pancreas transplant recipients are at greater risk for CMV infection than kidney and liver transplant recipients. Among the various clinical laboratory diagnostic tests currently available to detect CMV infection, nucleic acid amplification tests (eg, PCR) are the most sensitive and specific detection methods. In addition, quantification of CMV DNA level in peripheral blood (ie, CMV viral load) is used routinely to determine when to initiate preemptive antiviral therapy, diagnose active CMV disease, and monitor response to antiviral therapy. A number of factors can affect CMV viral load results, including the specimen type (whole blood versus plasma), biologic properties of CMV, performance characteristics of the quantitative assay (eg, limit of detection, limits of quantification, linearity, and reproducibility), degree of immunosuppression, and intensity of antiviral therapy. In general, higher CMV viral loads are associated with tissue-invasive disease, while lower levels are associated with asymptomatic infection. However, the viral load in the peripheral blood compartment may be low or undetectable in some cases of tissue-invasive disease. Since a wide degree of overlap exists in CMV viral load and disease, a rise in viral load over time is more important in predicting CMV disease than a single viral load result at a given time point. Therefore, serial monitoring (eg, weekly intervals) of organ transplant recipients with quantitative CMV PCR is recommended in such patients at risk for CMV disease. Since changes in viral load may be delayed by several days in response to antiviral therapy and immunosuppression, viral load should not be monitored more frequently than a weekly basis. Typically, CMV viral load changes of greater than 0.5 log IU/mL are considered biologically significant changes in viral replication. Patients with suppression of CMV replication (ie, viral load of <35 or <1.54 log IU/mL at days 7, 14, and 21 of treatment) had shorter times to resolution of clinical disease than those without viral suppression. No degree of relative viral load reduction from pretreatment level was associated with faster resolution of CMV disease.

**Useful For:** Detection and quantification of cytomegalovirus (CMV) viremia Monitoring CMV disease progression and response to antiviral therapy

**Interpretation:** The quantification range of this assay is 35 to 10,000,000 IU/mL (1.54 log to 7.00 log IU/mL), with a 95% or higher limit of detection at 35 IU/mL. A result of “Undetected” indicates the absence of cytomegalovirus (CMV) DNA in the plasma (see Cautions below). A result of “<35 IU/mL (<1.54 log IU/mL)” indicates that CMV DNA is detected in the plasma, but the assay cannot accurately quantify the CMV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the level of CMV DNA (ie, viral load) present in the plasma. A result of “>10,000,000 IU/mL (>7.00 log IU/mL)” indicates that CMV DNA level present in plasma is above 10,000,000 IU/mL (7.00 log IU/mL), and the assay cannot accurately quantify CMV DNA present above this level.

**Reference Values:**
Undetected

**Clinical References:**

**CMVNG 603607 Cytomegalovirus (CMV) Drug Resistance, Next-Generation Sequencing, Plasma**

**Clinical Information:** Cytomegalovirus (CMV) is a DNA virus with a seroprevalence of...
approximately 50% in the United States. Acute infection can be asymptomatic or cause a mononucleosis-like illness in immunocompetent individuals. After acute infection, the virus enters a latent state. Reactivation of the virus can occur, particularly if a patient becomes immunosuppressed. Immunocompromised patients are also at higher risk of severe acute infection. CMV disease may range from congenital disease, retinitis, inflammation of the gastrointestinal tract, encephalitis, and pneumonia. Treatment for CMV typically involves antiviral drugs as well as decreasing the degree of immunosuppression (if applicable and medically advisable). Currently, anti-CMV drugs bind and inhibit either a viral kinase (UL97 gene product) or a viral DNA polymerase (UL54 gene product).

There are a number of assays available to test for the presence of CMV. Quantitative assays report the concentration of CMV DNA present and can be used to monitor the viral load in patients who are at risk of CMV disease as well as assess response to antiviral therapy. A rising CMV viral load (ie, increase of 0.5 log or more between samples) correlates with an increased risk of CMV disease and may indicate treatment failure (ie, due to antiviral resistance) if the patient is on appropriate therapy. Variants in UL97 and UL54 have been associated with antiviral resistance. This test uses next-generation sequencing (NGS) to analyze the sequence of UL97 and UL54. Identified variants are reported if they have been previously associated with CMV antiviral resistance and are present in at least 15% of the sequences analyzed. This assay uses a database of known resistance-associated variants that is periodically updated with new variants that are reported in the scientific literature.

**Useful For:** Detecting variants in the cytomegalovirus genes, UL97 and UL54, which are associated with antiviral resistance

**Interpretation:** If a resistance-associated variant is detected, a patient's antiviral regimen may need to be adjusted for optimal response. If no resistance-associated variants are detected, it is still important to assess the patient's clinical response and quantitative viral load before determining that the infecting virus is susceptible to a treatment regimen (see Cautions). Predicted drug resistance is reported separately for each antiviral drug. Predicted resistance to one antiviral may or may not be associated with predicted cross-resistance to other drugs.

**Reference Values:**
None Detected/Not Predicted

**Clinical References:**

### Cytomegalovirus (CMV) Immunostain, Technical Component Only

**Clinical Information:** Cytomegalovirus (CMV) stain visualizes the intranuclear and cytoplasmic viral inclusions of CMV-infected cells. CMV can cause severe systemic infection (primary or reactivated infection) in patients who are immunocompromised. Antibodies to cytomegalovirus fail to react with any normal human tissue.

**Useful For:** Identification of cytomegalovirus infection

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call

Cytomegalovirus (CMV), Molecular Detection, PCR, Varies

Clinical Information: Infection with cytomegalovirus (CMV) is a significant cause of morbidity and mortality in transplant recipients and other immunocompromised hosts. Specific neurologic syndromes associated with CMV infection include subacute radiculomyelopathy, peripheral neuropathy, and encephalitis. CMV-associated central nervous system (CNS) disease occurs most commonly in immunocompromised patients. Histologic evidence of CMV infections in autopsy brain tissue was identified in 20% to 40% of AIDS patients. In 2 separate studies, CMV (DNA) was the most common herpesvirus (29/181, 16/49) detected from cerebrospinal fluid of patients with AIDS. CNS infections with CMV can also occur in immunocompetent patients. CMV is a leading cause of congenital viral infections worldwide, and laboratory testing by real-time PCR is useful in the diagnosis of neonatal CMV disease.

Useful For: Rapid qualitative detection of cytomegalovirus (CMV) DNA This test is not intended for the monitoring of cytomegalovirus (CMV) disease progression.

Interpretation: Detection of cytomegalovirus (CMV) DNA in a specimen supports the clinical diagnosis of infection due to this virus. Studies indicate that CMV DNA is not detected by PCR in cerebrospinal fluid from patients without central nervous system disease caused by this virus.

Reference Values:


Cytomegalovirus IgG Avidity

Clinical Information: Discrimination between recent (primary) and past cytomegalovirus (CMV) infection can be an important tool in the clinical management of pregnant women. Although nearly all individuals with recent CMV infection are positive for CMV IgM, individuals with past CMV may also express CMV IgM due to long-term IgM persistence or viral reactivation; thus, detection of CMV IgM is not a reliable indicator of recent CMV infection. Measurement of CMV IgG avidity can assist in
Discriminating recent from past CMV infection. A low avidity index is a reliable indicator of CMV infection within the previous 6 months, a high avidity index essentially excludes the possibility that infection occurred within the previous 4 months. Avidity index values should be considered within the context of other laboratory findings and clinical signs.

**Interpretation:**
- < 0.60: Low Avidity Index
- 0.60 - 0.70: Intermediate Avidity Index
- > 0.70: High Avidity Index

**Reference Values:**
- > 0.70
- < 0.60

**ANCA (9441)**

**Cytoplasmic Neutrophil Antibodies, Serum**

**Clinical Information:** Antineutrophil cytoplasmic antibodies (ANCA) can occur in patients with autoimmune vasculitis including Wegener granulomatosis (WG), microscopic polyangiitis (MPA), or organ-limited variants thereof such as pauci-immune necrotizing glomerulonephritis. Detection of ANCA is a well-established diagnostic test for the evaluation of patients suspected of having autoimmune vasculitis. ANCA react with enzymes in the cytoplasmic granules of human neutrophils including proteinase 3 (PR3), myeloperoxidase (MPO), elastase, and cathepsin G. Antibodies to PR3 occur in patients with WG (both classical WG and WG with limited end-organ involvement) and produce a characteristic pattern of granular cytoplasmic fluorescence on ethanol-fixed neutrophils called the cANCA pattern. Antibodies to MPO occur predominately in patients with MPA and produce a pattern of perinuclear cytoplasmic fluorescence on ethanol-fixed neutrophils called the pANCA pattern.

**Useful For:** Antineutrophil cytoplasmic antibodies (cANCA and pANCA):
- Evaluating patients suspected of having autoimmune vasculitis (both Wegener granulomatosis [WG] and microscopic polyangiitis) cANCA titer:
- May be useful for monitoring treatment response in patients with WG (systemic or organ-limited disease); increasing titer suggests relapse of disease, while a decreasing titer suggests successful treatment

**Interpretation:** Positive results for antineutrophil cytoplasmic antibodies (cANCA or pANCA) are consistent with the diagnosis of Wegener granulomatosis (WG), either systemic WG with respiratory and renal involvement or limited WG with more restricted end-organ involvement. Positive results for pANCA are consistent with the diagnosis of autoimmune vasculitis including microscopic polyangiitis (MPA) or pauci-immune necrotizing glomerulonephritis. Sequential measurements of titers of cANCA may be useful to indicate the clinical course of patients with WG. Changes in titer of 2 or more serial dilutions are considered significant.

**Reference Values:**
- Negative
- If positive for antineutrophil cytoplasmic antibodies, results are titered.

**Clinical References:**

**DDITT (40936)**

**D-Dimer, Plasma**

**Clinical Information:** The specific degradation of fibrin (ie, fibrinolysis) is the reactive mechanism responding to the formation of fibrin. Plasmin is the fibrinolytic enzyme derived from inactive plasminogen. Plasminogen is converted into plasmin by plasminogen activators. The main plasminogen
activators are tissue plasminogen activator (tPA) and pro-urokinase, which is activated into urokinase (UK) by, among others, the contact system of coagulation. In the bloodstream, plasmin is rapidly and specifically neutralized by alpha-2-antiplasmin, thereby restricting its fibrinogenolytic activity and localizes the fibrinolysis on the fibrin clot. On the fibrin clot, plasmin degrades fibrin into various products (ie, D-dimers). Antibodies specific for these products, which do not recognize fibrinogen, have been developed. The presence of these various fibrin degradation products, among which D-dimer is the terminal product, is the proof that the fibrinolytic system is in action in response to coagulation activation. Elevated D-dimer levels are found in association with disseminated intravascular coagulation (DIC), pulmonary embolism (PE), deep vein thrombosis (DVT), trauma, and bleeding. D-dimer may also be increased in association with pregnancy, liver disease, malignancy, inflammation, or a chronic hypercoagulable state.

Useful For: Excluding the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability(1-4) Diagnosis of intravascular coagulation and fibrinolysis, also known as disseminated intravascular coagulation, especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time)(5)

Interpretation: A normal D-dimer result of 500 ng/mL or less fibrinogen equivalent units (FEU) on the IL D-Dimer HS500 kit has a negative predictive value of approximately 100% (range 97%-100%) and is FDA approved for the exclusion of acute pulmonary embolism (PE) and deep vein thrombosis (DVT) when there is low or moderate pretest probability for PE or DVT. D-dimer concentrations increase with age and, therefore, the specificity for DVT and PE exclusion decreases with age. For DVT or PE exclusion, in addition to clinical pretest probability, age-adjusted D-dimer cutoffs are suggested for patients older than 50 years of age. Recent evidence suggests using clinical pretest probability and age-adjusted cutoffs to improve the performance of D-dimer testing in patients older than 50 years of age. In recent studies, when compared to a fixed D-dimer cutoff, age-adjusted D-dimer cutoff values (calculated as follows: age [years] x 10 ng/mL) resulted in equivalent outcomes and no additional false negative findings.(6-7) Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: -Clinical or subclinical disseminated intravascular coagulation/intravascular coagulation and fibrinolysis -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism -Association with pregnancy, liver disease, inflammation, malignancy, or hypercoagulable (procoagulant) states The degree of D-dimer increase does not definitely correlate with the clinical severity of associated disease states.

Reference Values:
< or =500 ng/mL Fibrinogen Equivalent Units (FEU)
D-dimer values < or =500 ng/mL FEU may be used in conjunction with clinical pretest probability to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).

D-Dimer, Plasma

Clinical Information: Thrombin, the terminal enzyme of the plasma procoagulant cascade, cleaves fibrinopeptides A and B from fibrinogen, generating fibrin monomer. Fibrin monomer contains D domains on each end of the molecule and a central E domain. Most of the fibrin monomers polymerize to form insoluble fibrin, or the fibrin clot, by repetitive end-to-end alignment of the D domains of 2 adjacent molecules in lateral contact with the E domain of a third molecule. The fibrin clot is subsequently stabilized by thrombin-activated factor XIII, which covalently cross-links fibrin monomers by transamidation, including dimerization of the D domains of adjacent fibrin monomers. The fibrin clot promotes activation of fibrinolysis by catalyzing the activation of plasminogen (by plasminogen activators) to form plasmin enzyme. Plasmin proteolytically degrades cross-linked fibrin, ultimately producing soluble fibrin degradation products of various sizes that include cross-linked fragments containing neoantigenic D-dimer (DD) epitopes. Plasmin also degrades fibrinogen to form fragments X, Y, D, and E. D-dimer immunoassays use monoclonal antibodies to DD neoantigen and mainly detect cross-linked fibrin degradation products, whereas the fibrinolytic degradation products-X, Y, D, and E, and their polymers may be derived from fibrinogen or fibrin. Therefore, the blood content of D-dimer indirectly reflects the generation of thrombin and plasmin, roughly indicating the turnover or activation state of the coupled blood procoagulant and fibrinolytic mechanisms.(1)

Useful For: Diagnosis of intravascular coagulation and fibrinolysis (ICF), also known as disseminated intravascular coagulation (DIC), especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time) Exclusion of the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability

Interpretation: D-dimer values < or =500 ng/mL Â fibrinogen-equivalent units (FEU) are normal. Within the reportable normal range (220-500 ng/mL FEU), measured values may reflect the activation state of the procoagulant and fibrinolytic systems, but the clinical utility of such quantitation is not established. A normal D-dimer result (< or =500 ng/mL FEU) has a negative predictive value of approximately 95% for the exclusion of acute pulmonary embolism (PE) or deep vein thrombosis when there is low or moderate pretest PE probability. Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: -Clinical or subclinical disseminated intravascular coagulopathy (DIC)/intravascular coagulation and fibrinolysis (ICF). -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism. -Association with pregnancy, liver disease, inflammation, malignancy or hypercoagulable (procoagulant) states. The degree of D-dimer increase does not definitely correlate with the clinical severity of associated disease states.

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

< or =500 ng/mL Fibrinogen Equivalent Units (FEU)
D-dimer values < or =500 ng/mL FEU may be used in conjunction with clinical pretest probability to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).


**D-Lactate, Plasma**

**Clinical Information:** D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts of D-lactate are present, individuals can experience metabolic acidosis, altered mental status (from drowsiness to coma), and a variety of other neurologic symptoms, particularly dysarthria and ataxia. D-lactic acidosis is typically observed in patients with a malabsorptive disorder, such as short-bowel syndrome, or following a jejunooileal bypass. In addition, healthy children presenting with gastroenteritis may also develop the critical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, this test). However, as D-lactate is readily excreted in urine, DLAU / D-Lactate, Urine is the preferred specimen for D-lactate determinations.

**Useful For:** An adjunct to urine D-lactate (preferred) for the diagnosis of D-lactate acidosis

**Interpretation:** Increased levels are consistent with D-lactic acidosis. However, because D-lactate is readily excreted, urine determinations are preferred.

**Reference Values:**
0.0-0.25 mmol/L

**Clinical References:**

**D-Lactate, Urine**

**Clinical Information:** D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts are absorbed it can cause metabolic acidosis, altered mental status (from drowsiness to coma) and a variety of other neurologic symptoms, in particular dysarthria and ataxia. Although a temporal relationship has been described between elevations of plasma and urine D-lactate and the accompanying encephalopathy, the mechanism of neurologic manifestations has not been elucidated. D-lactic acidosis is typically observed in patients with short-bowel syndrome and following jejunoileal bypass resulting in carbohydrate malabsorption. In addition, healthy children presenting with gastroenteritis may also develop the critical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, DLAC / D-Lactate, Plasma). However, as D-lactate is readily excreted in urine, this is the preferred specimen for D-lactate determinations.

**Useful For:** Preferred test for diagnosing D-lactate acidosis, especially in patients with jejunoileal bypass and short-bowel syndrome

**Interpretation:** Increased levels are diagnostic.

**Reference Values:**
0.0-0.25 mmol/L

**Clinical References:**

**Dabigatran, Ecarin, Plasma**

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
Clinical Information: Dabigatran, an oral direct thrombin inhibitor (DTI) that directly inhibits factor IIa, is indicated for use in patients with nonvalvular atrial fibrillation and venous thromboembolism. Dabigatran is administered orally twice daily, is eliminated primarily through the renal system, and can inhibit both soluble and clot-bound thrombin. Dabigatran does not require routine therapeutic monitoring. However, in selected clinical situations, measurement of drug level would be useful, e.g., renal insufficiency, assessment of compliance, periprocedural, suspected overdose, advanced age, and extremes of body weight. Observed dabigatran steady-state exposure concentrations:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median trough levels (10-16 hours post dose)</th>
<th>Median peak levels (1-3 hours post dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 mg twice daily</td>
<td>64.7 ng/mL (28.2-155)</td>
<td>126 ng/mL (52-275)</td>
</tr>
<tr>
<td>150 mg twice daily</td>
<td>91 ng/mL (39.8-215)</td>
<td>175 ng/mL (74.3-383)</td>
</tr>
</tbody>
</table>

Venous thromboembolism:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median trough levels (10-16 hours post dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg twice daily</td>
<td>59.7 ng/mL (38.6-146)</td>
</tr>
</tbody>
</table>

Useful For: Measuring dabigatran concentration in plasma This assay is not useful for measurement of other direct thrombin inhibitors e.g., argatroban or bivalirudin.

Interpretation: Therapeutic reference ranges have not been established. See Clinical Information for peak and trough drug concentrations observed in clinical trials of dabigatran.

Reference Values:

<20 ng/mL

Clinical References:


Dairy and Grain Allergen Profile, Serum

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

Useful For: Establishing a diagnosis of an allergy to dairy and grain. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Dandelion, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to dandelion Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
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</table>

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

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

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.
Date, Tree, IgE, Serum

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

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

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

Reference Values:

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<tr>
<td>1</td>
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<tr>
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<td>0.70-3.49</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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</tbody>
</table>


Dedicator of Cytokinesis 8 (DOCK8) Deficiency, Blood

Clinical Information: Dedicator of cytokinesis 8 (DOCK8) is an atypical guanine exchange factor that plays a role in regulating actin polymerization and cytoskeletal rearrangement. DOCK8 is important in both innate and adaptive immunity by contributing to cellular migration, cytotoxicity, antibody production, and immunological memory. DOCK8 deficiency is a rare, combined immunodeficiency with an autosomal recessive inheritance that typically presents in childhood. Its clinical features include...
atopic disease, recurrent sinopulmonary infections, cutaneous viral infection, Staphylococcus aureus skin infections, and cancer. DOCK8 deficiency is diagnosed based on clinical phenotype, immunologic findings, and molecular analysis. Diseases in the differential diagnosis include Job syndrome (AD-HIES), ZNF341 deficiency, and severe atopic dermatitis. Assessment of DOCK8 expression on immune cells is an important component and facilitates the diagnosis of this condition and the timely treatment of the patient.

**Useful For:** Aids in the diagnosis of dedicator of cytokinesis 8 (DOCK8) deficiency

**Interpretation:** The results will be reported as the percentage of dedicator of cytokinesis 8 (DOCK8) expression on T cells, B cells, NK cells, and monocytes. The absence of DOCK8 expression on all cell types will be consistent with DOCK8 deficiency. In this case, genetic analysis of DOCK8 to confirm the diagnosis and to identify the underlying alteration will be recommended. The expression of DOCK8 on a subset of T cells and/or NK cells could suggest somatic reversion in a patient with DOCK8 deficiency, which can modulate disease phenotype over time.

**Reference Values:** The appropriate reference values will be provided on the report.

**Clinical References:**

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**Dehydroepiandrosterone (DHEA), Serum**

**Clinical Information:** Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). The bulk of DHEA is secreted as a 3-sulfoconjugate dehydroepiandrosterone sulfate (DHEAS). Both hormones are albumin bound, but DHEAS binding is much tighter. As a result, circulating concentrations of DHEAS are much higher (>100-fold) compared to DHEA. In most clinical situations, DHEA and DHEAS results can be used interchangeably. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEAS back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA/DHEAS and their 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA/DHEAS levels fall by 80% or more and remain low until the onset of adrenarche at age 7 or 8 in girls and age 8 or 9 in boys. Adrenarche is a poorly understood phenomenon, peculiar to higher primates, that is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not casually linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults and some boys may develop early penile enlargement. Following adrenarche, DHEA/DHEAS levels increase until the age of 20 to a maximum roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown, and trials of DHEA/DHEAS replacement in older individuals have not produced convincing benefits. However, in younger and older patients with primary adrenal failure, the addition of DHEA/DHEAS to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA/DHEAS levels can cause signs or symptoms of hyperandrogenism in women. Men are usually asymptomatic but, through peripheral

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conversion of androgens to estrogens, can occasionally experience mild estrogen excess. Most mild-to-moderate elevations in DHEAS levels are idiopathic. However, pronounced elevations of DHEA/DHEAS may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid dehydrogenase deficiency is associated with excessive DHEA/DHEAS production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein (STAR) or 17 alpha-hydroxylase deficiency is characterized by low DHEA/DHEAS levels. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnosing and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) As an initial screen in adults with bioavailable testosterone measurement. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin and occasionally other androgenic steroids (eg, 17-hydroxyprogesterone). An adjunct in the diagnosis of congenital adrenal hyperplasia (CAH); DHEA/DHEAS measurements play a secondary role to the measurements of cortisol/cortisone, 17 alpha-hydroxyprogesterone, and androstenedione Diagnosing and differential diagnosis of premature adrenarche

**Interpretation:** Elevated dehydroepiandrosterone (DHEA)/dehydroepiandosterone sulfate (DHEAS) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels 5-fold or more of the upper limit of normal can suggest the presence of an androgen-secreting adrenal tumor. DHEA/DHEAS levels are elevated in greater than 90% of patients with such tumors. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce downstream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA/DHEAS. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA/DHEAS, often 5-fold to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA/DHEAS measurements. Consequently, DHEA/DHEAS testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA/DHEAS level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA/DHEAS levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. See Steroid Pathways in Special Instructions.

**Reference Values:**

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<tbody>
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</tr>
<tr>
<td>0-1 day</td>
<td>&lt;11 ng/mL*</td>
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<tr>
<td>2-6 days</td>
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<td>7 days-1 month</td>
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<tr>
<td>&gt;1-23 months</td>
<td>&lt;2.9 ng/mL*</td>
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<tr>
<td>2-5 years</td>
<td>&lt;2.3 ng/mL</td>
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<td>6-10 years</td>
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<td>&gt; or =61 years</td>
<td>&lt;5.0 ng/mL</td>
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For SI unit Reference Values, see [https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html](https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html)

Dehydroepiandrosterone Sulfate, Serum

Clinical Information: Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone. The bulk of DHEA is secreted as a 3-sulfoconjugate (DHEA-S). Both hormones are albumin bound, but binding of DHEA-S is much tighter. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEA-S back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA-S and its 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA-S levels fall by 80% or more and remain low until the onset of adrenarche. Adrenarche is a poorly understood phenomenon peculiar to higher primates, which is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not causally linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization and is generally regarded as a benign condition, not needing intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Following adrenarche, DHEA-S levels increase until the age of 20, up to maximum levels roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA-S replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA-S to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA-S levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild to moderate elevations in DHEA-S levels are idiopathic. However, pronounced elevations of DHEA-S may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid deficiency is associated with excessive DHEA-S production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein or 17 alpha-hydroxylase deficiencies are characterized by low DHEA-S levels. An initial workup in adults might also include total and bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) and, occasionally other androgenic steroids (eg, 17-hydroxyprogesterone).

Useful For: Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An adjunct in the diagnosis of congenital adrenal hyperplasia Diagnosis and differential diagnosis of premature adrenarche

Interpretation: Elevated dehydroepiandrosterone sulfate (DHEA-S) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels of 600 mcg/dL or more can suggest the presence of an androgen-secreting adrenal tumor. DHEA-S levels are elevated in more than 90% of patients with such tumors, usually well above 600 mcg/dL. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce down-stream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA-S. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA-S, often 5- to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better
diagnostic accuracy than DHEA-S measurements. Consequently, DHEA-S testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA-S level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA-S levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. Girls below the age of 7 to 8 and boys before age 8 to 9, who present with early development of pubic hair, or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty or both.

Measurement of DHEA-S (DHEAS / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), dehydroepiandrosterone (DHEA / Dehydroepiandrosterone [DHEA], Serum), and androstenedione (ANST / Androstenedione, Serum), alongside determination of sensitive estradiol (EEST / Estradiol, Serum), testosterone and bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum), or free testosterone (TGRP / Testosterone, Total and Free, Serum), sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum), and luteinizing hormone (LH / Luteinizing Hormone [LH], Serum)/follicle-stimulating hormone (FSH / Follicle-Stimulating Hormone [FSH], Serum) levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. Levels of DHEA-S do not show significant diurnal variation. Many drugs and hormones can result in changes in DHEA-S levels. Whether any of these secondary changes in DHEA-S levels are of clinical significance and how they should be related to the established normal reference ranges is unknown. In most cases, the drug-induced changes are not large enough to cause diagnostic confusion, but when interpreting mild abnormalities in DHEA-S levels, drug and hormone interactions should be taken into account. Examples of drugs and hormones that can reduce DHEA-S levels include: insulin, oral contraceptive drugs, corticosteroids, central nervous system agents that induce hepatic enzymes (eg, carbamazepine, clomipramine, imipramine, phenytoin), many antilipemic drugs (eg, statins, cholestyramine), dopaminergic drugs (eg, levodopa/dopamine, bromocryptine), fish oil, and vitamin E. Drugs that may increase DHEA-S levels include: metformin, troglitazone, prolactin, (and by indirect implication many neuroleptic drugs), danazol, calcium channel blockers (eg, diiltiazem, amlodipine), and nicotine.

### Reference Values:

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<th>Mean</th>
<th>Age</th>
<th>Reference Range (mcg/dL)</th>
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<tbody>
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<td>Stage I</td>
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<td>11-120</td>
</tr>
<tr>
<td>Stage II</td>
<td>11.5 years</td>
<td>14-323</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>5.5-312</td>
</tr>
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<td>Stage IV</td>
<td>15.1 years</td>
<td>29-412</td>
</tr>
<tr>
<td>Stage V</td>
<td>18.0 years</td>
<td>104-468 <em>Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-) 2 years. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) is usually reached by age 18. 18-30 years: 105-728 mcg/dL 31-40 years: 57-522 mcg/dL 41-50 years: 34-395 mcg/dL 51-60 years: 20-299mcg/dL 61-70 years: 12-227 mcg/dL &gt; or =71 years: 6.6-162 mcg/dL FEMALES 1-14 days: DHEA-S levels in newborns are very elevated at birth but fall to prepubertal levels within a few days. Tanner Stages</em>Â</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>Age</th>
<th>Reference Range (mcg/dL)</th>
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</table>
### Clinical References:

### Delta-Like 3 Protein (SP347), Semi-Quantitative Immunohistochemistry, Manual, Tissue

**Clinical Information:** Delta-like 3 protein (DLL3) is an atypical Notch ligand induced by the neuroendocrine transcription factor, ASCL-1. DLL3 is expressed on the cell membrane and in the cytoplasm of tumor cells.

**Useful For:** Diagnosis of small cell lung carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), amongst other tumors

**Interpretation:** Positivity for this test will require 50% or more of the tumor cells within a specimen to express delta-like 3 protein with an intensity ranging from 1 to 3+.

**Clinical References:**

### Dementia, Autoimmune Evaluation, Serum
Clinical Information: The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy-responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms such as personality change, executive dysfunction, and psychiatric symptoms are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized within a triad of: 1) suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings, 2) the detection of cerebrospinal fluid (CSF) or serological biomarkers of autoimmunity and 3) a response to immunotherapy. Detection of neural autoantibodies in serum or CSF serves 2 purposes; to inform the physician of a likely autoimmune etiology and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, LGI1 antibody was initially considered to be specific for autoimmune limbic encephalitis, but over time other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1: ANNA-1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5-IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has CRMP-5-IgG, and subsequent reflex reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful, particularly when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and GFAP-IgG) because CSF testing is both more sensitive and specific.

Useful For: Investigating new onset dementia and cognitive impairment plus 1 or more of the following using serum specimens: -Rapid onset and progression -Fluctuating course -Psychosis, hallucinations -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -Smoking history (20+ pack years) or other cancer risk factors -History of cancer -Inflammatory cerebrospinal fluid -Neuroimaging findings atypical for degenerative etiology

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-aminobutyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

Reference Values:
<table>
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<tr>
<th>Test ID</th>
<th>Reporting name</th>
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**Clinical References:**
Dementia, Autoimmune Evaluation, Spinal Fluid

Clinical Information: The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy-responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms such as personality change, executive dysfunction, and psychiatric symptoms are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized within a triad of: 1) suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings, 2) the detection of cerebrospinal fluid (CSF) or serological biomarkers of autoimmunity and 3) a response to immunotherapy. Detection of neural autoantibodies in serum or CSF serves 2 purposes; to inform the physician of a likely autoimmune etiology and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, LGI1 antibody was initially considered to be specific for autoimmune limbic encephalitis, but over time other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example: small-cell lung carcinoma (antineuronal nuclear antibody-type 1: ANNA-1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5 IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has CRMP-5-IgG, and subsequent reflex reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful particularly when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and GFAP-IgG) because CSF testing is both more sensitive and specific.

Useful For: Investigating new onset dementia and cognitive impairment plus 1 or more of the following accompaniments using cerebrospinal fluid specimens: - Rapid onset and progression - Fluctuating course - Psychiatric accompaniments (psychosis, hallucinations) - Movement disorder (myoclonus, tremor, dyskinesias) - Headache - Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) - Smoking history (20+ pack years) or other cancer risk factors - History of cancer - Inflammatory cerebrospinal fluid - Neuroimaging findings atypical for degenerative etiology

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: - Plasma membrane antibodies (N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor). These autoantibodies are all potential effectors of dysfunction. - Neuronal nuclear autoantibody type 1 (ANNA-1) or type 3 (ANNA-3). - Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).
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**Clinical References:**

**DCME**
**Dendritic Cell and Monocyte Enumeration, Blood**
**Clinical Information:** Dendritic cells (DC) play a critical role in both innate and adaptive immune
responses. DC include 2 major subsets: myeloid (or conventional) dendritic cells (mDC) and plasmacytoid dendritic cells (pDC). mDC can capture and present antigens to CD4+ T cells and cross-present them to CD8+ T cells. They are also a source of inflammatory cytokines. pDC take part in priming of antiviral T cells and are the major source of type I interferons; as such they act as a primary defense against viremia. Monocytes are the archetypal myeloid mononuclear cells. Although human monocytes do have phenotypic heterogeneity, the majority are CD14+ and are classified as classical or inflammatory monocytes. The list of conditions where this test can be used as part of the assessment include, but are not limited to, GATA-binding protein 2 (GATA2) deficiency, IKZF1 deficiency, IRF8 deficiency, STAT3 gain-of-function disease, HYOU1 deficiency, reticular dysgenesis due to AK2 variants, WHIM syndrome, dedicator of cytokinesis 8 (DOCK8) deficiency, IRF7 deficiency and Hermansky-Pudlak syndrome type II. In addition, unexplained monocytopenia can be a relevant clue in detecting DC deficiency.

**Useful For:** Aiding in the diagnosis of patients suspected of defects in innate immunity, particularly those involving monocyte and dendritic cell development This test has not been validated for the diagnosis of hematologic malignancies.

**Interpretation:** Interpretive comments will be provided, where applicable, to complement the reported plasmacytoid dendritic cells, myeloid (or conventional) dendritic cells, and monocyte counts and their respective reference ranges.

**Reference Values:**
The appropriate reference values will be provided on the report.

**Clinical References:**

**Dengue Virus Antibody, IgG and IgM, Serum**

**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease annually. Following dengue infection, the incubation period varies from 3 to 7 days and, while some infections remain asymptomatic, the majority of individuals will develop classic dengue
fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM and IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure and, therefore, testing of acute and convalescent sera may be necessary to make the diagnosis. As an adjunct to serologic testing, identification of early DV infection may be made by detection of the DV nonstructural protein 1 (NS1) antigen. NS1 antigenemia is detectable within 24 hours of infection and up to 9 days following symptom onset. The DV NS1 antigen can be detected by ordering DNSAG / Dengue Virus NS1 Antigen, Serum.

**Useful For:** Aiding in the diagnosis of dengue virus infection

**Interpretation:** The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens collected too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, collected approximately 10 to 12 days following exposure should be tested.

**Reference Values:**
- IgG: negative
- IgM: negative

Reference values apply to all ages.

**Clinical References:**

**DENVP 62869 Dengue Virus Antibody/Antigen Panel, Serum**

**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM and IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure and therefore testing of acute and convalescent sera may be necessary to make the diagnosis. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic- and molecular-based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation (as performed in this profile) for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV provides optimal diagnostic potential for both early and late dengue disease.
Useful For: Aiding in the diagnosis of dengue virus infection by detection of IgM and IgG antibodies and the nonstructural protein 1 (NS1)

Interpretation: The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens collected too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, collected approximately 10 to 12 days following exposure should be tested. The presence of dengue nonstructural protein 1 (NS1) antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative in samples collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

Reference Values:
IgG: negative
IgM: negative
NS1: negative
Reference values apply to all ages.


Dengue Virus NS1 Antigen, Serum

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected, and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days, and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic and molecular based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV (DENG M / Dengue Virus Antibody, IgG and IgM, Serum) provides optimal diagnostic potential for both early and late dengue disease.

Useful For: Aiding in the diagnosis of dengue virus infection

Interpretation: Positive: The presence of dengue nonstructural protein 1 (NS1) antigen is consistent
with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). Negative: The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative if specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

Reference Values:
Negative
Reference values apply to all ages.

**Clinical References:**

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**Dengue Virus, Molecular Detection, PCR, Serum**

**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of DV nucleic acid in serum is a marker of acute infection with this virus. Importantly, the period of time that the virus can be detected in serum is brief and, therefore, molecular testing should be performed within the first week following onset of symptoms. After this time, serologic testing is the preferred method for diagnosis of DV infection.

**Useful For:** Aiding in the diagnosis of acute infection caused by dengue virus

**Interpretation:** Positive: The detection of dengue virus nucleic acid in serum is consistent with acute-phase infection. Dengue virus nucleic acid may be detectable during the first 1 to 7 days following the onset of symptoms. Negative: The absence of dengue nucleic acid in serum is consistent with the lack of acute-phase infection. Dengue virus nucleic acid may not be detected if the serum specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 7 days of symptoms.

**Reference Values:**
Negative

**Clinical References:**
**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of DV nucleic acid in cerebrospinal fluid (CSF) is a marker for central nervous system infection caused by this virus. Importantly, the period of time that the virus can be detected in serum and CSF is brief and, therefore, molecular testing should be performed within the first week following onset of symptoms. After this time, serologic testing is the preferred method for diagnosis of DV infection.

**Useful For:** Aiding in the diagnosis of central nervous system infection caused by dengue virus

**Interpretation:**
- **Positive:** The detection of dengue virus nucleic acid in cerebrospinal fluid (CSF) is consistent with acute-phase infection of the central nervous system. Dengue virus nucleic acid may be detectable during the first 1 to 7 days following the onset of symptoms.
- **Negative:** The absence of dengue nucleic acid in CSF is consistent with the lack of acute-phase infection. Dengue virus nucleic acid may not be detected if the CSF specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 7 days of symptoms.

**Reference Values:**
Negative

**Clinical References:**

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**Dentatorubral-Pallidoluysian Atrophy (DRPLA) Gene Analysis, Varies**

**Clinical Information:** Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder characterized by ataxia, choreoathetosis, dementia, and psychiatric disturbance in adults and ataxia, myoclonus, seizures, and progressive intellectual deterioration in children. Characteristic neuropathologic observations include degeneration of the dentatorubral and pallidoluysian systems of the central nervous system. The prevalence of DRPLA depends on the geographic and ethnic origin of the population being studied. DRPLA was first described in a European individual without a family history; however, it is predominantly found as an inherited condition and is most prevalent in Japan (0.2-0.7 per 100,000). Although rare, DRPLA has been identified in other populations including Europe and North America. DRPLA is caused by an expansion of the CAG trinucleotide repeat in the ATN1 (DRPLA) gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 7 to 35. In affected individuals the CAG expansion ranges from 48 to 93 repeats. As with other trinucleotide repeat disorders, anticipation is frequently observed, and larger CAG expansions are associated with earlier onset and a more severe and rapid clinical course. In DRPLA, the observed anticipation appears to be significantly greater in paternal transmissions.

**Useful For:** Molecular confirmation of a diagnosis of dentatorubral-pallidoluysian atrophy (DRPLA) for symptomatic patients Predictive testing for individuals with a family history of DRPLA and a documented expansion in the ATN1 gene in an affected family member

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Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Interpretation:** An interpretive report will be provided.

**Reference Values:**

- Normal alleles: 7-35 CAG repeats
- Abnormal alleles: 49-93 CAG repeats

An interpretive report will be provided.

**Clinical References:**

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**Deoxypyridinoline Crosslinks, Urine**

**Reference Values:**

- Deoxypyridinoline Urine-ratio to CRT
  - Adult Male: 2.3–8.7 nmol/mmol
  - Premenopausal Adult Female: 3.1–8.7 nmol/mmol

- Creatinine, Urine Å–ã¢â€œ per volume

  No reference interval

The target value for treated post-menopausal adult females is the same as the Premenopausal reference interval.

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**Dermatophagoides microceras, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Dermatophagoides microceras

Defining the allergen responsible for eliciting signs and symptoms

Identifying allergens: Responsible for allergic disease and/or anaphylactic episode

To confirm sensitization prior to beginning immunotherapy

To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

- Class IgE kU/L

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<th>Class</th>
<th>Interpretation</th>
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<tbody>
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DermPath Consultation, Wet Tissue

Clinical Information: Dermatopathology involves histologic examination of skin biopsy and oral mucosal specimens.

Useful For: Histologic diagnosis and differential diagnosis of cutaneous diseases

Interpretation: Histologic diagnosis is based primarily on interpretation of hematoxylin and eosin-stained sections. Special histochemical stains, such as alcian blue, Giemsa, or periodic acid-Schiff may be necessary in some cases. Interpretation is based on evaluation of patterns including architectural and cytologic details, which are included in a microscopic description.

Reference Values: Diagnosis and description of microscopic findings


Des-Gamma-Carboxy Prothrombin, Serum

Clinical Information: Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many hepatocellular carcinoma (HCC) cells, and an abnormal prothrombin with all or some of unconverted glutamic acid is secreted. Therefore, this noncarboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to alpha fetoprotein (AFP) and third electrophoretic form of lentil lectin-reactive AFP% (AFP-L3%) for assessing the risk of developing HCC. The elevation of both AFP-L3 and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3%, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3%, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion and/or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because
of this, a normal DCP value does not rule out HCC.

**Useful For:** Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma (HCC) Aiding in the monitoring of HCC patients post therapy if des-gamma-carboxy prothrombin (DCP) level was elevated prior to therapy

**Interpretation:** In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing hepatocellular carcinoma (HCC) is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%). For patients with HCC and an elevated DCP level prior to therapy, an elevated DCP level posttherapy is associated with an increased risk of HCC recurring.

**Reference Values:**
<7.5 ng/mL

**Clinical References:**

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**Desipramine, Serum**

**Clinical Information:** Desipramine is a tricyclic antidepressant; it also is a metabolite of imipramine. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects: dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations in excess of 400 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 400 ng/mL.

**Useful For:** Monitoring serum concentration of desipramine during therapy Evaluating potential desipramine toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with levels above 400 ng/mL.

**Reference Values:**
Therapeutic concentration: 100-300 ng/mL

Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose).
Levels may be elevated in non-trough specimens.

**Clinical References:**
**DESMN**

**Desmin Immunostain, Technical Component Only**

**Clinical Information:** Desmin is an intermediate filament protein in striated and smooth muscle cells. In neoplastic tissues, the antibody reacts with tumors of myogenic origin such as those arising from smooth muscle (leiomyosarcomas) and those derived from striated muscle (rhabdomyosarcomas).

**Useful For:** Identification of striated and smooth muscle cells and tumors derived from this cell type

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**DSGAB**

**Desmoglein 1 (DSG1) and Desmoglein 3 (DSG3), IgG Antibodies, Serum**

**Clinical Information:** Pemphigus includes a group of often fatal autoimmune blistering diseases characterized by intraepithelial lesions. Pemphigus vulgaris and its variants may present with oral or mucosal lesions alone or with mucosal plus skin lesions. Pemphigus foliaceous and variants present with skin lesions alone. Indirect immunofluorescence (IIF) studies reveal that both forms of pemphigus are caused by autoantibodies to cell surface antigens of stratified epithelia or mucous membranes and skin. These antibodies bind to calcium-dependent adhesion molecules in cell surface desmosomes, notably desmoglein 1 (DSG1) in pemphigus foliaceus and desmoglein 3 (DSG3) and/or DSG1 in pemphigus vulgaris. Desmogleins are protein substances located in and on the surface of keratinocytes. These proteins have been shown to be a critical factor in cell-to-cell adhesion. Antibodies to desmogleins can result in loss of cell adhesion, the primary cause of blister formation in pemphigus. The diagnosis of pemphigus depends on biopsy and serum studies that characterize lesions and detect the autoantibodies that cause them. Originally, the serum studies were performed by IIF using monkey esophagus and other tissue substrates. The identification of the reactive antigens as DSG1 and DSG3 has made it possible to develop highly specific and sensitive enzyme-linked immunosorbent assay methods.

**Useful For:** Preferred screening test for patients suspected to have an autoimmune blistering disorder of the skin or mucous membranes (pemphigus) Aiding in the diagnosis of pemphigus

**Interpretation:** Antibodies to desmoglein 1 (DSG1) and desmoglein 3 (DSG3) have been shown to be present in patients with pemphigus. Many patients with pemphigus foliaceous, a superficial form of pemphigus have antibodies to DSG1. Patients with pemphigus vulgaris, a deeper form of pemphigus, have antibodies to DSG3 and sometimes DSG1 as well. Antibody titer correlates in a semiquantitative manner with disease activity in many patients. Patients with severe disease can usually be expected to have high titers of antibodies to DSG. Titers are expected to decrease with clinical improvement. Our experience demonstrates a very good correlation between DSG1 and DSG3 results and the presence of pemphigus. Adequate sensitivities and specificity for disease are documented. However, in those...
patients strongly suspected to have pemphigus either by clinical findings or by routine biopsy, and in whom the DSG assay is negative, the indirect immunofluorescence (CIFS / Cutaneous Immunofluorescence Antibodies [IgG], Serum) is recommended.

**Reference Values:**
DESMOLEIN 1
<20 RU/mL (negative)
> or =20 RU/mL (positive)

DESMOLEIN 3
<20 RU/mL (negative)
> or =20 RU/mL (positive)

**Clinical References:**

**DESG3**

**Desmoglein 3 (DSG3) Immunostain, Technical Component Only**

**Clinical Information:** Desmoglein 3 (DSG3) is a calcium-binding transmembrane glycoprotein component of desmosomes in vertebrate epithelial cells. Currently, three desmoglein subfamily members have been identified and all are members of the cadherin cell adhesion molecule superfamily. Positivity for DSG3 in a non-small cell lung carcinoma supports a diagnosis of squamous cell carcinoma.

**Useful For:** Classification of squamous cell carcinomas

**Interpretation:** This test does not includes pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FDXM**

**Dexamethasone**

**Reference Values:**
Units = ng/dL

Current as of June 14, 2021 12:13 pm CDT
**FDXAP 57720**  
**Dexedrine (Dextroamphetamine)**  
**Reference Values:**  
Reference Range: 10 - 100 ng/mL

**FDM 90117**  
**Dextromethorphan (DM), Serum**  
**Reference Values:**  
Reference Range: 2.0 - 6.0 ng/mL

**DBS1 48400**  
**Diabetes Mellitus Type 1 Evaluation, Serum**  
**Clinical Information:** Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus since the 1970s. Since 1988, several autoantigens against which islet antibodies are directed have been identified. These include the insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin, and, most recently, the zinc transporter ZnT8.(1) Only 4% to 7% of patients with type 1 diabetes are autoantibody negative, fewer than 10% have only 1 marker, and around 70% have 3 or 4 markers. These findings have been confirmed in multiple specialty laboratories internationally. One or more of these autoantibodies are detected in 93% to 96% of patients with type 1 diabetes, both adults and children. These antibodies are also detectable in relatives of type 1 diabetic patients at risk for developing diabetes, before clinical onset.(2) Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom-onset in adulthood, societal obesity, and initial insulin-independence. These patients with either "latent autoimmune diabetes in adulthood" or type 1 diabetes mellitus may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including ZnT8 antibody). Patients with gestational diabetes can also be stratified for future diabetes risk by detection of 1 or more islet autoantibodies.

**Useful For:** Distinguishing type 1 from type 2 diabetes mellitus  
Identifying individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes)  
Predicting future insulin requirement treatment in patients with adult-onset diabetes

**Interpretation:** Seropositivity for 1 or more islet cell autoantibodies is supportive of:  
-A diagnosis of type 1 diabetes. Only 2% to 4% of patients with type 1 diabetes are antibody negative; 90% have more than 1 antibody marker, and 70% have 3 or 4 markers.(1) Patients with gestational diabetes who are antibody seronegative are at high risk for diabetes postpartum. Rarely, diabetic children test seronegative, which may indicate a diagnosis of maturity-onset diabetes of the young in clinically suspicious cases.  
-A high risk for future development of diabetes. Among 44 first-degree relatives of patients with type 1 diabetes, those with 3 antibodies had a 70% risk of developing type 1 diabetes within 5 years.(2)  
-A current or future need for insulin therapy in patients with diabetes. In the UK Prospective Diabetes Study, 84% of those classified clinically as having type 2 diabetes and seropositive for glutamic acid decarboxylase 65 required insulin within 6 years, compared to 14% that were antibody negative.(3)

**Reference Values:**  
**GLUTAMIC ACID DECARBOXYLASE (GAD65) ANTIBODY**  
< or =0.02 nmol/L  
Reference values apply to all ages.  
**INSULIN ANTIBODIES**  
< or =0.02 nmol/L  
Reference values apply to all ages.  
**ISLET ANTIGEN 2 (IA-2) ANTIBODY**  
< or =0.02 nmol/L  
Reference values apply to all ages.  
**ZINC Transporter 8 (ZnT8) ANTIBODY**  
< 15.0 U/mL  
Reference values apply to all ages.

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**DIA**

**8629**

**Diazepam and Nordiazepam, Serum**

**Clinical Information:** Diazepam, a benzodiazepine derivative, is an anxiolytic agent that reduces neuronal depolarization resulting in decreased action potentials. It enhances the action of gamma-amino butyric acid (GABA) by tightly binding to A-type GABA receptors, thus opening the membrane channels and allowing the entry of chloride ions. It is also used as a muscle relaxant, procedural sedation agent, and sedative-hypnotic agent to treat withdrawal states (ie, ethanol), along with other conditions (seizures). Diazepam is metabolized to several metabolites in the liver including temazepam, oxazepam, and nordiazepam (desmethyldiazepam), and the clearance of the drug is reduced considerably in older individuals and in patients with hepatic disease. Therapeutic assessment typically includes measurement of both the parent drug (diazepam) and the active metabolite (nordiazepam).

**Useful For:** Assessing compliance Monitoring for appropriate therapeutic level Assessing diazepam toxicity

**Interpretation:** For seizures: Serum concentrations are not usually monitored during early therapy because response to the drug can be monitored clinically as seizure control. If seizures resume despite adequate therapy, another anticonvulsant must be considered. Toxicity is commonly seen when diazepam plus nordiazepam concentrations exceed 3000 ng/mL. Adverse effects of benzodiazepines in therapeutic doses usually reflect the drug’s pharmacology and include sedation, slurred speech, and ataxia. Respiratory depression/arrest may occur with large overdoses or following rapid intravenous injection with short-acting benzodiazepines.

**Reference Values:**
Therapeutic concentrations
Diazepam and Nordiazepam: 200-2,500 ng/mL


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**FDICH**

**75393**

**Dichloromethane, Serum**

**Clinical Information:** Exposure to 200 ppm (TLV) in air for two hours produced up to 2.0 mcg/mL blood.

**Reference Values:**
Reporting limit determined each analysis
Units: mcg/mL

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**FDGTX**

**75374**

**Digitoxin, Serum**

**Reference Values:**
Reporting limit determined each analysis.

Digitoxin
Therapeutic Range: Â· 10 - 30 ng/mL
Digoxin, Free, Serum

Clinical Information: Digoxin, a widely prescribed cardiac drug, has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue concentrations). While excess digoxin can have serious side effects (eg, cardiac dysrhythmias, heart failure, seizures, death), it is one of the few therapeutic drugs for which antidotal therapy is available. In toxic situations, antibody fragment therapy, which involves the administration of antibodies to digoxin (eg, Digibind, Digoxin Immune Fab), is indicated. In manufacturing of Digibind, papain cleaves digoxin-specific IgG antibody into 2 antigen binding-site fragments (Fab fragments). These fragments bind to digoxin, block the active site of the digoxin molecule, and make it unavailable to its receptor molecule and biologically inactive. The Fab fragment-digoxin complex is then excreted by the kidney. Total digoxin concentration in blood increases approximately 10 to 30 fold after administration of Fab fragments. On the other hand, the unbound (free) fraction, which is responsible for its pharmacological activity, decreases. Traditional digoxin assays performed by immunoassay (eg, DIG / Digoxin, Serum) measure both Fab fragment-bound (inactive) digoxin and free (active) digoxin (ie, total digoxin), and are unsuitable for managing patients when digoxin-specific Fab fragment therapy has been administered. Assays for measurement of free digoxin levels only are necessary in such situations. The kidneys provide the main route of Fab fragment elimination from the body. In patients with normal renal function, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of 15 to 20 hours. Ordinarily, improvement in signs or symptoms of digoxin intoxication begins within a half hour or less after initiation of Fab fragment therapy. Clearance may be delayed in patients with renal failure. In such patients, toxicity may recur if previously bound drug is released from the Fab fragments, resulting in increased levels of free digoxin. Digoxin-like immunoreactive factors (DLIFs) are endogenous substances that can cross-react with testing antibodies used in some digoxin immunoassays, causing erroneous results. DLIFs may be seen in certain volume-expanded patients such as neonates, patients with renal or liver disease, and in women in the third trimester of pregnancy being treated with digoxin. DLIFs are strongly bound to proteins and, in this assay, are removed prior to testing. The following ordering guidelines are offered: -When creatinine clearance is less than 30 mL/min/surface area: order free digoxin levels daily for 12 days (or until dismissal) -When creatinine clearance is equal to or above 30 mL/min/surface area (and the patient is not on renal-replacement therapy): order free levels daily for 72 hours, as long as the last level is not supratherapeutic (these patients are expected to have good clearance and a lower risk for reintoxication) -Also order total digoxin levels every other day during the time periods above, with a goal of determining whether there is correlation between changes in free and total levels.

Useful For: Evaluating recrudescent (breakthrough) digoxin toxicity in renal-failure patients Assessing the need for more antidigoxin Fab to be administered Deciding when to reintroduce digoxin therapy Monitoring patients with possible digoxin-like immunoreactive factors (DLIFs)

Interpretation: The target therapeutic level is 0.4 to 0.9 ng/mL. Toxicity may be seen when free digoxin concentrations are 3.0 ng/mL or higher. Pediatric patients may tolerate higher concentrations. Therapeutic concentrations for free digoxin are 25% lower than therapeutic values for total digoxin due to the separation of protein-bound digoxin in the assay.

Reference Values:
<16 years:
Therapeutic ranges have not been established for patients who are under 16 years of age. In adults, the suggested serum free digoxin therapeutic range is 0.4-0.9 ng/mL.
Toxic concentration: > or =3.0

> or =16 years:
0.4-0.9 ng/mL
Toxic concentration: > or =3.0 ng/mL

Digoxin, Serum

Clinical Information: Compounds in the digitalis family of glycosides consist of a steroid nucleus, a lactone ring, and a sugar. Digoxin is widely prescribed for the treatment of congestive heart failure and various disturbances of cardiac rhythm. Digoxin improves the strength of myocardial contraction, and results in the beneficial effects of increased cardiac output, decreased heart size, decreased venous pressure, and decreased blood volume. Digoxin therapy also results in stabilized and slowed ventricular pulse rate. These therapeutic effects are produced through a network of direct and indirect interactions upon the myocardium, blood vessels, and the autonomic nervous system. Digoxin is well absorbed after oral administration and is widely distributed to tissues, especially the heart, kidney, and liver. A number of factors can alter normal absorption, distribution, and bioavailability of the drug, including naturally occurring enteric bacteria in the bowel, presence of food in the gut, strenuous physical activity, ingestion of quinine or quinidine, and concomitant use of a wide range of drugs. Children generally require higher concentrations of digoxin. After oral administration, there is an early rise in serum concentration. Equilibration of serum and tissue levels occurs at approximately 6 to 8 hours. For this reason, blood specimens for digoxin analysis should be drawn at least 6 to 8 hours after drug administration. Digoxin is excreted primarily in the urine. The average elimination half-life is 36 to 40 hours but may be considerably prolonged in those with renal disease, causing digoxin accumulation and toxicity. Symptoms of digoxin toxicity often mimic the cardiac arrhythmia's for which the drug was originally prescribed (e.g., heart block and heart failure). Other typical symptoms of toxicity include gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal pain and diarrhea, and neuropsychologic symptoms, such as fatigue, malaise, dizziness, clouded or blurred vision, visual and auditory hallucination, paranoid ideation, and depression. Toxicity of digoxin may reflect several factors: the drug has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue levels); individuals vary in their ability to metabolize and respond to digoxin; absorption of various oral forms of digoxin may vary over a 2-fold range; susceptibility to digitalis toxicity apparently increases with age.

Useful For: Monitoring digoxin therapy

Interpretation: The therapeutic range is 0.6 to 1.2 ng/mL. Levels of 4.0 ng/mL and above may be potentially life-threatening.

Reference Values:

<16 years:
Therapeutic ranges have not been established for patients who are less than 16 years of age.

> or =16 years:
Therapeutic range: 0.6-1.2 ng/mL
Toxic concentration: > or =4.0 ng/mL

Dihydropyrimidine Dehydrogenase Genotype, Varies

Clinical Information: 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation. This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity. Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment. In addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation. The following table displays the DPYD variants detected by this assay, the corresponding star allele, and the effect on DPYD enzyme activity. Other or novel variations, besides those listed here, may also impact fluoropyrimidine-related side effects and tumor response. DPYD allele cDNA nucleotide change Effect on enzyme activity *1 None (wild type) Normal activity *2A 1905+1G>A No activity *7 299_302delTCAT No activity *8 703C>T No activity *10 2983G>T No activity *13 1679T>G No activity rs67376798 2846A>T Decreased activity rs75017182 1129-5923C>G Decreased activity rs115232898 557A>G Decreased activity

Useful For: Identifying individuals with genetic variants in DPYD who are at increased risk of toxicity when prescribed 5-fluorouracil (5-FU) or capecitabine chemotherapy treatment

Interpretation: An interpretive report will be provided. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical Information: 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation (table 1). This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity. Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment. In addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation. Table 1. Known Genetic Variations Associated with Fluoropyrimidine Treatment Gene cDNA numbering Alternative name Enzyme activity Phenotype? DPYD No variations identified *1 c.1905+1G->A *2A No activity or significantly reduced activity High risk for fluoropyrimidine toxicity c.1679T->G *13 c.1898delC *3 c.299_302delTCAT *7 c.1156G->T *12 c.2846A->T rs67376798 Reduced activity Increased risk for fluoropyrimidine toxicity c.1129-5923C->G rs75017182 c.703C->T *8 Probable reduced function Increased risk for fluoropyrimidine toxicity c.2983G->T *10 c.1003G->T *11 c.557A->G rs115232898 c.1601C->T *4 Normal activity** Normal risk for fluoropyrimidine toxicity c.1627A->G *5 c.2194C->T *6 c.85T->C *9A *Other or novel variations, besides those listed here, may also impact fluoropyrimidine-related side effects and tumor response and will be reported if detected. **Alleles that are categorized as having normal enzyme activity (eg, *4, *5, *6, *9A) will not be reported if detected because variants with normal enzyme activity are not expected to impact fluoropyrimidine-related side effects and tumor response. The DPYD gene is located on chromosome 1 and contains 2 transcripts. The longer transcript (NM_000110.3) contains 23 exons, and the shorter transcript (NM_001160301.1) contains 6 exons, with exon 6 being unique to this transcript. All exons from the longer transcript (NM_000110.3) and exon-intron boundaries are assessed. Genetic variations involved in the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes including toxicity and tumor response.

Useful For: Identifying individuals at increased risk of toxicity when considering 5-fluorouracil and capecitabine chemotherapy treatment. May be useful in identifying variants associated with decreased or absent dihydropyrimidine dehydrogenase enzyme activity for an individual with this deficiency suspected.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values: An interpretive report will be provided.

**Dihydrorhodamine Flow Cytometric N-Formyl-Methionyl-Leucyl-Phenylalanine Test, Blood**

**Clinical Information:** This assay can be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory mutations in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function.(1) Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with phorbol myristate acetate (PMA), indicating normal NADPH oxidase activity, but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, indicates a signaling defect in Rac2 deficiency.(2)

**Useful For:** Diagnosis of Rac2 deficiency

**Interpretation:** An interpretive report will be provided, in addition to the quantitative values described in Clinical Information. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after N-formyl-methionyl-leucyl-phenylalanine stimulation, and the mean fluorescence intensity.

**Reference Values:**

<table>
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<tr>
<th>Result Name</th>
<th>Unit</th>
<th>Cutoff for defining normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% fMLP ox-DHR+</td>
<td>%</td>
<td>&gt; or =10%</td>
</tr>
<tr>
<td>MFI fMLP ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =2</td>
</tr>
<tr>
<td>Control % fMLP ox-DHR+</td>
<td>%</td>
<td>&gt; or =10%</td>
</tr>
<tr>
<td>Control MFI fMLP ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =2 The appropriate age-related reference values for Absolute Neutrophil Count will be provided on the report.</td>
</tr>
</tbody>
</table>

fewer infections. There is significant clinical variability even among individuals with similar mutations, 
in terms of NADPH oxidase function, indicating that there can be several modulating factors including 
the genetic defect, infection history, and granulomatous and autoimmune complications. There appears 
to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can 
treated with hematopoietic cell transplantation (HCT), which can be effective for the inflammatory and 
autoimmune manifestations. It has been shown that survival of patients with CGD was strongly 
associated with residual reactive oxygen intermediate (ROI) production, independent of the specific 
gene defect.(4) Measurement of NADPH oxidase activity through the dihydrorhodamine (DHR) flow 
cytometry assay contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD 
includes evaluation of NADPH oxidase function in neutrophils, using either the nitroblue tetrazolium 
test (NBT) or the more analytically sensitive DHR test, as described here. Activation of neutrophils with 
phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 
123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different 
genetic forms of CGD.(5, 6) Complete myeloperoxidase (MPO) deficiency can cause a false-positive 
result for CGD in the DHR flow cytometric assay (7); however, there is a difference between the 
percent DHR+ neutrophils and the mean fluorescence intensity (MFI) after PMA stimulation that allows 
discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of 
recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD 
neutrophils.(7) It is important to have quantitative measures in the DHR flow cytometry assay to 
effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimerism 
and NADPH oxidase activity post-HCT. These quantitative measures include assessment of the relative 
proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the 
relative fluorescence intensity of DHR (MFI) on neutrophils after activation. Female carriers of 
X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome 
inactivation).(8) Age-related acquired skewing of lyonization can also cause increased susceptibility to 
inflections in carriers of X-linked CGD.(9) While germline mutations are more common in CGD, there 
have been reports of de novo, sporadic mutations in the CYBB gene, causing X-linked CGD in male 
patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been 
reported in patients with X-linked CGD who have small populations of normal cells.(10) There are also 
reports of triple somatic mosaicism in female carriers (11,12) as well as late-onset disease in an adult 
female who was a somatic mosaic for a novel mutation in the CYBB gene.(13) Therefore, the clinical, 
genetic, and age spectrum of CGD is varied and laboratory assessment of NADPH oxidase activity after 
neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate 
diagnosis or for monitoring patients posttransplant.

Useful For: Diagnosis of chronic granulomatous disease (CGD), X-linked and autosomal recessive 
forms, complete myeloperoxidase (MPO) deficiency; monitoring chimerism and nicotinamide adenine 
dinucleotide phosphate (NADPH) oxidase function posthematopoietic cell transplantation Assessing 
residual NADPH oxidase activity posttransplant Identification of carrier females for X-linked CGD; 
assessment of changes in lyonization with age in carrier females

Interpretation: An interpretive report will be provided, in addition to the quantitative values described 
in Clinical Information. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow 
cytometric assay has to include both the proportion of positive neutrophils for DHR after phorbol 
myristate acetate stimulation, and the mean fluorescence intensity. Additionally, visual assessment of the 
pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated 
with chronic granulomatus disease and complete myeloperoxidase deficiency.

Reference Values:

<table>
<thead>
<tr>
<th>Result Name</th>
<th>Unit</th>
<th>Cutoff for defining normal</th>
</tr>
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<tbody>
<tr>
<td>% PMA ox-DHR+</td>
<td>%</td>
<td>&gt; or =95%</td>
</tr>
<tr>
<td>MFI PMA ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =60</td>
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<td>Control % PMA ox-DHR+</td>
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<tr>
<td>Control MFI PMA ox-DHR+</td>
<td>MFI</td>
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DHR

Dihydrorhodamine Flow Cytometric Test, Blood

Clinical Information: Chronic granulomatous disease (CGD) is caused by genetic defects in the gene components that encode the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. These defects result in an inability to produce superoxide anions required for killing bacterial and fungal organisms. Other clinical features include a predisposition to systemic granulomatous complications and autoimmunity.(1) There are 5 known genetic defects associated with the clinical phenotype of CGD.(2) The gene defects include mutations in the CYBB gene, encoding the gp91phox protein, which is X-linked and accounts for approximately 70% of CGD cases. Other gene defects are autosomal recessive: NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), and NCF4 (p40phox). Typically, patients with X-linked CGD have the most severe disease, while patients with p47phox defects tend to have the best outcomes. Mutations in NCF4 encoding the p40phox protein have been the most recently described(3) and appears to be associated with more gastrointestinal disease with fewer infections. There is significant clinical variability even among individuals with similar mutations, in terms of NADPH oxidase function, indicating that there can be several modulating factors including the genetic defect, infection history, and granulomatous and autoimmune complications. There appears to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can be treated with hematopoietic cell transplantation (HCT), which can be effective for the inflammatory and autoimmune manifestations. It has been shown that survival of patients with CGD was strongly associated with residual reactive oxygen intermediate (ROI) production, independent of the specific gene defect.(4) Measurement of NADPH oxidase activity through the dihydrorhodamine (DHR) flow cytometry assay contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD includes evaluation of NADPH oxidase function in neutrophils, using either the nitroblue tetrazolium test (NBT) or the more analytically sensitive DHR test, as described here. Activation of neutrophils with phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD.(5, 6) Complete myeloperoxidase (MPO) deficiency can cause a false-positive result for CGD in the DHR flow cytometric assay (7); however, there is a difference between the percent DHR+ neutrophils and the mean fluorescence intensity (MFI) after PMA stimulation that allows discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of
recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD neutrophils.(7) It is important to have quantitative measures in the DHR flow cytometry assay to effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimerism and NADPH oxidase activity post-HCT. These quantitative measures include assessment of the relative proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the relative fluorescence intensity of DHR (MFI) on neutrophils after activation. This assay can also be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory mutations in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and NADPH oxidase function.(8) Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with PMA, indicating normal NADPH oxidase activity, but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, indicates a signaling defect in Rac2 deficiency.(9) Female carriers of X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome inactivation).(10) Age-related acquired skewing of lyonization can also cause increased susceptibility to infections in carriers of X-linked CGD.(11) While germline mutations are more common in CGD, there have been reports of de novo, sporadic mutations in the CYBB gene, causing X-linked CGD in male patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been reported in patients with X-linked CGD who have small populations of normal cells.(12) There are also reports of triple somatic mosaicism in female carriers (13,14) as well as late-onset disease in an adult female who was a somatic mosaic for a novel mutation in the CYBB gene.(15) Therefore, the accurate, genetic, and age spectrum of CGD is varied and laboratory assessment of NADPH oxidase activity after neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate diagnosis or for monitoring patients posttransplant.

**Useful For:** Diagnosis of chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, Rac2 deficiency, complete myeloperoxidase (MPO) deficiency; monitoring chimerism and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function posthematopoietic cell transplantation Assessing residual NADPH oxidase activity pretransplant Identification of carrier females for X-linked CGD; assessment of changes in lyonization with age in carrier females

**Interpretation:** An interpretive report will be provided, in addition to the quantitative values. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after phorbol myristate acetate (PMA) and/or N-formyl-methionyl-leucyl-phenylalanine (fMLP) stimulation, and the mean fluorescence intensity (MFI). Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease (CGD) and complete myeloperoxidase (MPO) deficiency.

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<tr>
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<td>MFI</td>
<td>&gt; or =2 The appropriate age-related reference values for Absolute Neutrophil Count will be provided on the report.</td>
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</table>

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DHTS

Dihydrotestosterone, Serum

Clinical Information: The principal prostatic androgen is dihydrotestosterone (DHT). Levels of DHT remain normal with aging, despite a decrease in the plasma testosterone, and are not elevated in benign prostatic hyperplasia (BPH). (1) DHT is generated by reduction of testosterone by 5-alpha reductase. Two isoenzymes of 5-alpha reductase have been discovered. Type 1 is present in most tissues in the body where 5-alpha reductase is expressed, and is the dominant form in sebaceous glands. Type 2 is the dominant isoenzyme in genital tissues, including the prostate. Androgenetic alopecia (AGA; male-pattern baldness) is a hereditary and androgen-dependent progressive thinning of the scalp hair that follows a defined pattern. (2) While the genetic involvement is pronounced, but poorly understood, major advances have been achieved in understanding the principal elements of androgen metabolism that are involved. DHT may be related to baldness. High concentrations of 5-alpha reductase have been found in frontal scalp and genital skin and androgen-dependent processes are predominantly due to the binding of DHT to the androgen receptor (AR). Since the clinical success of treatment of AGA with modulators of androgen metabolism or hair growth promoters is limited, sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of AGA. Currently available AGA treatment modalities with proven efficacy are oral finasteride, a competitive inhibitor of 5-alpha reductase type 2, and topical minoxidil, an adenosine triphosphate-sensitive potassium channel opener that has been reported to stimulate the production of vascular endothelial growth factor in cultured dermal papilla cells. Currently, many patients with prostate disease receive treatment with a 5-alpha reductase inhibitor such as finasteride (Proscar) to diminish conversion of DHT from testosterone. See Steroid Pathways in Special Instructions.

Useful For: Monitoring patients receiving 5-alpha reductase inhibitor therapy or chemotherapy Evaluating patients with possible 5-alpha reductase deficiency

Interpretation: Patients taking 5-alpha reductase inhibitor have decreased dihydrotestosterone (DHT) serum levels. Patients with genetic 5-alpha reductase deficiency (a rare disease) also have...
reduced DHT serum levels. DHT should serve as the primary marker of peripheral androgen production. However, because it is metabolized rapidly and has a very high affinity for sex hormone-binding globulin (SHBG), DHT does not reflect peripheral androgen action. Instead, its distal metabolite, 3-alpha, 17-beta-androstanediol glucuronide, serves as a better marker of peripheral androgen action. See Steroid Pathways in Special Instructions.

**Reference Values:**

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<th>Reference range (pg/mL)</th>
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<tr>
<td>Stage II</td>
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<td>Stage III</td>
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<td>Stage IV</td>
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<td>220-520</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>240-650</td>
</tr>
</tbody>
</table>

Females

< 6 months: < or =50 pg/mL

> 6 months: < or =1,200 pg/mL

Tanner Stages

< or =50 pg/mL

< or =6 months: < or =1,200 pg/mL

< or =1,200 pg/mL

**Clinical References:**


**Clinical Information:**

The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy...
may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC). DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias, and conduction system disease, or thromboembolic disease (stroke). The most recent estimates of the incidence of DCM suggest that the condition affects approximately 1 in every 250 people. These estimates are higher than originally reported due to subclinical phenotypes and underdiagnosis. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. The majority of familial dilated cardiomyopathy is inherited in an autosomal dominant manner; however, autosomal recessive and X-linked forms have also been reported. At least 28 genes have been reported in association with DCM, including genes encoding the cardiac sarcomere and other proteins involved in proteins responsible for cardiac muscle contraction. Some genes associated with DCM also cause other forms of hereditary cardiomyopathy, cardiac channelopathies, skeletal myopathies, or metabolic defects. See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Dilated Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ABCC9 ATP-Binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD DCM, DES Danon disease LAM A4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated membrane protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MYBPC3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH6 Myosin, heavy chain 6, cardiac muscle, alpha HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYPN Myopalladin AD HCM, DCM, NEXN Nexilin AD HCM, DCM PLN Phospholamban AD DCM, RAFT1 V-raft-1 murine leukemia viral oncogene homolog 1 AD Noonan/multiple lentigines syndrome, DCM RRM20 RNA-binding motif protein 20 AD DCM SCN5A Sodium channel, voltage gated, type V, alpha subunit AD Brugada syndrome, DCM, Heart block, LQTS, SSS, SIDS SGCD Sarcoglycan, delta AD, AR DCM, LGMD TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TCAP Titin-CAP (Telethonin) AD, AR HCM, DCM, LGMD TNRC1 Troponin C, slow AD HCM, DCM TNNT3 Troponin I, cardiac AD, AR DCM, HCM, RCM TNNT2 Troponin T2, cardiac AD HCM, DCM, RCM, LVNC TPM1 Tropomyosin 1 AD HCM, DCM, LVNC, TTN Titin AD, AR HCM, DCM, ARVC myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinclunin AD HCM, DCM Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), congenital heart defects (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary dilated cardiomyopathy (DCM) Establishing a diagnosis of a hereditary DCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease features that allows for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional judgment.
**Dill, IgE, Serum**

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

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

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

**Reference Values:**

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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
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FDILT 91118

Diltiazem (Cardizem, Dilacor)

Reference Values:
Reference Range: 50 - 200 ng/mL

DRVI3 602181

Dilute Russell Viper Venom Time (DRVVT) Confirmation Ratio, Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of one or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT) and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or to help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing. With the reflexive testing, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. It is advisable to use the DRVVT screen, mix, and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in
vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Confirming the presence or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

**Reference Values:**
Only orderable as part of a reflex. For more information see DRVII / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma.

<1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

**Clinical References:**
Dilute Russell Viper Venom Time (DRVVT) Confirmation, Plasma

Clinical Information: Dilute Russell viper venom time (DRVVT) confirmation is only performed when the DRVVT screen is abnormally prolonged. Refer to DRV1 / Dilute Russell Viper Venom Time (DRVVT), Plasma for interpretation of results.

Useful For: Confirming the presence or absence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

Interpretation: Dilute Russell viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio >1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions). Additional tests to evaluate abnormal DRVVT results include activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time. Abnormalities observed with these tests may be further evaluated with normal plasma mixing studies, the platelet neutralization procedure (for APTT), and coagulation factor assays may sometimes be needed. All of these reflexive testing procedures, together with Coagulation Consultant interpretation, are included in Mayo Clinic's Coagulation Consultation test panels: ALUPP / Lupus Anticoagulant Profile, Plasma ALBLD / Bleeding Diathesis Profile, Limited, Plasma AATHR / Thrombophilia Profile, Plasma APROL / Prolonged Clot Time Profile, Plasma ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

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

<1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for
newborn infants whose results may not reach adult values until 3 to 6 months of age.

**Clinical References:**
6. CLSI Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A.

**Dilute Russell Viper Venom Time (DRVVT) Interpretation**

**Clinical Information:**
Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT) and DRVVT. If the PT, APTT, or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). Â The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or to help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT Screen Ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing. With a reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. It is advisable to use the DRVVT screen, mix and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing...
panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Interpreting mixing and confirmation assays for lupus anticoagulants (LA)

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirm ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) Because no single coagulation test can identify or exclude all LAs, and because of the complexity of testing LA, one of the following Coagulation Consultation reflexive panel procedures are recommended if clinically indicated: ALUPP / Lupus Anticoagulant Profile, Plasma AATHR / Thrombophilia Profile, Plasma APROL / Prolonged Clot Time Profile. Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

**Reference Values:**
Only orderable as a part of a profile. For more information see DRVI1 / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma.

**Clinical References:**
combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylycerine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta2GPI) or clotting factors including prothrombin (factor II) or factor X, and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time [APTT], dilute Russell viper venom time [DRVVT]) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT), and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell’s viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or to help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing. With the reflexive testing, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. It is advisable to use the DRVVT screen, mix and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Detecting the presence or helping to exclude the presence of lupus anticoagulants (LA)
Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the activated partial thromboplastin time (APTT) or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results include the following:
- DRVVT screen ratio $\geq 1.20$, DRVVT mix ratio $< 1.20$, and DRVVT confirmation ratio $< 1.20$: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. - DRVVT screen ratio $\geq 1.20$, DRVVT mix ratio $\geq 1.20$, and DRVVT confirmation ratio $< 1.20$: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of $< 1.20$ makes this less likely. - DRVVT screen ratio $\geq 1.20$, DRVVT mix ratio $< 1.20$, and DRVVT confirmation ratio $\geq 1.20$: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. - DRVVT screen ratio $\geq 1.20$, DRVVT mix ratio $\geq 1.20$, and DRVVT confirmation ratio $\geq 1.20$: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) Because no single coagulation test can identify or exclude all LAs, and because of the complexity of testing LA, one of the following Coagulation Consultation reflexive panel procedures are recommended if clinically indicated: ALUPP / Lupus Anticoagulant Profile, Plasma AATHR / Thrombophilia Profile, Plasma APROL / Prolonged Clot Time Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

Reference Values:
Only orderable as part of a reflex. For more information see DRVII / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma.

$< 1.20$
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Clinical References:

**Dilute Russell Viper Venom Time (DRVVT) Mix, Plasma**

**Clinical Information:** Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable antiphospholipid antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on...
Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT) and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or to help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing. With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Detecting the presence or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

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procedure (for APTT), and coagulation factor assays may sometimes be needed. All of these reflexive testing procedures, together with Coagulation Consultant interpretation, are included in Mayo Clinic’s Coagulation Consultation test panels: ALUPP / Lupus Anticoagulant Profile, Plasma ALBLD / Bleeding Diathesis Profile, Limited, Plasma AATHR / Thrombophilia Profile, Plasma APROL / Prolonged Clot Time Profile, Plasma ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

Reference Values:
Only orderable as part of a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
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AATHR / Thrombophilia Profile, Plasma
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

<1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.


Dilute Russell Viper Venom Time (DRVVT), Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable antiphospholipid antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT) and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma.
(to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). Â The venom obtained from Russell’s viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or to help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing (see Testing Algorithm). With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Detecting and confirming or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20 and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results include the following:Â -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) Additional tests to evaluate abnormal DRVVT results include activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time. Abnormalities observed with these tests may be further evaluated with normal plasma mixing studies, the platelet neutralization procedure (for APTT), and coagulation factor assays may sometimes be needed. All of these reflexive testing procedures, together with Coagulation Consultant interpretation, are included in Mayo Clinic's Coagulation Consultation test panels (ALUPP / Lupus Anticoagulant Profile), Plasma ALBLD / Bleeding Diathesis Profile, Limited), Plasma AATHR / Thrombophilia Profile), Plasma APROL / Prolonged Clot Time Profile), Plasma ADIC / Disseminated Intravascular Coagulation/ Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile), Plasma DRVVT assays ordered as a single, stand-alone test should be
interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

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

< 1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.


DRVI1

602179

Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation testing is recommended, including the prothrombin time (PT), APTT, thrombin time (TT), and the DRVVT. If the PT, APTT, or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine the presence or absence of anticoagulants or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from the Russell viper (Viperus russelli) contains enzymes that directly activate coagulation
factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests that have a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm the presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or to help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing (see Testing Algorithm). With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. It is advisable to use the DRVVT screen, mix and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Detecting and confirming or helping to exclude the presence of lupus anticoagulants (LA)
Identifying LA that do not prolong the activated partial thromboplastin time (APTT)
Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests
Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulants (LA) is not present, or not detectable, by this method (but might be detected with other methods). Abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest the presence of LA; however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired. -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirm ratios). Possible combinations of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirm ratio <1.20: No evidence of LA. This data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirm ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects, or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease, etc. Although LA cannot be conclusively excluded, the DRVVT confirm ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirm ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirm ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirm ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions). Because no single coagulation test can identify or exclude all LAs, and because of the complexity of testing LA, a combination or panel of coagulation tests is recommended: ALUPP / Lupus Anticoagulant Profile, Plasma AATHR / Thrombophilia Profile, Plasma APRoL / Prolonged Clot Time Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

**Reference Values:**
Dilute Russell viper venom time screen ratio <1.20
Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

**Clinical References:**
DIPGS 36664

Diphtheria Toxoid IgG Antibody, Serum

Clinical Information: Diphtheria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx and posterior nasal passages. C diphtheriae produces a potent diphtheria exotoxin that is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diphtheria toxoid, which stimulates antidiphtheria toxoid antibodies. In the United States, diphtheria toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. A patient's immunological response to diphtheria toxoid vaccination can be determined by measuring antidiaphtheria toxoid IgG antibody using this enzyme immunoassay technique. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Determining a patient's immunological response to diphtheria toxoid vaccination Aiding in the evaluation of immunodeficiency

Interpretation: Results of 0.01 IU/mL or more suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with antidiaphtheria toxoid IgG values between 0.01 and less than 0.1 IU/mL.

Reference Values:
- Vaccinated: Positive (≥0.01 IU/mL)
- Unvaccinated: Negative (<0.01 IU/mL)

Reference values apply to all ages.


DTABS 36670

Diphtheria/Tetanus Antibody Panel, Serum

Clinical Information: Diphtheria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx, and posterior nasal passages. C diphtheriae produces a potent diphtheria exotoxin that is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diphtheria toxoid, which stimulates antidiaphtheria toxoid antibodies. In the United States, diphtheria toxoid is administered to children as part of the combined diphtheria, tetanus, acellular pertussis (TDaP) vaccine. A patient's immunological
response to diphtheria toxoid vaccination can be determined by measuring antidualphtheria toxoid IgG antibody using this enzyme immunoassay technique. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs. Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin, tetanospasmin. Tetanospasmin attaches to peripheral nerve endings and travels to the central nervous system (CNS) where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospasmin), which stimulates development of antitetanus toxoid antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, acellular pertussis (TDaP) vaccine. Two to 3 weeks following vaccination, a patient's immunological response may be assessed by measuring the total antitetanus toxoid IgG antibody level in serum. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

**Useful For:** Assessment of an antibody response to tetanus and diphtheria toxoid vaccines, which should be performed at least 3 weeks after immunization. Aiding in the evaluation of immunodeficiency. This test should not be used to diagnose tetanus infection.

**Interpretation:** Diphtheria: Results of 0.01 IU/mL or more suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with antidiphtheria toxoid IgG values between 0.01 and less than 0.1 IU/mL. Tetanus: Results of 0.01 IU/mL or more suggest a vaccine response. A tetanus toxoid booster should strongly be considered for patients with antitetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients who have a measurable serum level of 0.01 to 1.0 IU/mL.

**Reference Values:**

**DIPHTHERIA TOXOID IgG ANTIBODY**

- Vaccinated: Positive (≥0.01 IU/mL)
- Unvaccinated: Negative (<0.01 IU/mL)

Reference values apply to all ages.

**TETANUS TOXOID IgG ANTIBODY**

- Vaccinated: Positive (≥0.01 IU/mL)
- Unvaccinated: Negative (<0.01 IU/mL)

Reference values apply to all ages.


**Direct Antiglobulin Test (Polyspecific), Blood**

**Clinical Information:** IgG antibody or complement components secondary to the action of IgM antibody may be present on the patient’s own RBCs or on transfused RBCs.

**Useful For:** Demonstrating in vivo coating of RBCs with IgG or the complement component C3d in...
the following settings: -Autoimmune hemolytic anemia -Hemolytic transfusion reactions -Drug-induced hemolytic anemia

**Interpretation:** Negative: No IgG antibody or complement (C3d) detected on the surface of the red cell. Positive: Test DATR will be ordered and performed.

**Reference Values:**
Negative
If positive, test DATR will be performed.


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**DSAC 608236**

**Disaccharidase Activity Panel, Tissue**

**Clinical Information:** Disaccharidases in the small intestines are responsible for the breakdown of disaccharides (double sugars) into monosaccharides (simple sugars). Patients with a deficiency of 1 or more disaccharidase enzymes can experience intolerance to foods containing complex sugars resulting in a range of gastrointestinal symptoms including diarrhea or constipation, abdominal pain and cramping, gas, bloating, and nausea. In addition, patients may experience malnutrition, weight loss, or failure to thrive. Given the nonspecificity and frequency of abdominal symptoms, misdiagnosis or a diagnostic delay of disaccharide deficiencies may occur. Primary and secondary causes of disaccharidase deficiencies exist, and age of onset may vary from birth through adulthood. Primary causes are rare and result from genetic alterations in a variety of genes. Secondary deficiencies typically result from small intestinal mucosal damage. Treatment of both primary and secondary disaccharidase deficiencies involves dietary management. While primary deficiencies require lifelong treatment, secondary disaccharidase deficiencies may require treatment only until the intestinal lining recovers.

**Useful For:** Evaluation of patients who present with signs or symptoms suggestive of disaccharidase disorders

**Interpretation:** Quantitative values of lactase, sucrase, maltase, palatinase, and glucoamylase are reported. Clinical interpretation of results is provided.

**Reference Values:**
Lactase: <14.0 nM/min/mgram protein (abnormal)
Sucrase: <19.0 nM/min/mgram protein (abnormal)
Maltase: <70.0 nM/min/mgram protein (abnormal)
Palatinase: <6.0 nM/min/mgram protein (abnormal)
Glucoamylase: <8.0 nM/min/mgram protein (abnormal)


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**FDSAC 91414**

**Disaccharidase Analysis**

**Reference Values:**
Lactase: Range 24.5 +/- 8.0
Abnormal <15.0

Units = uM/min/gram protein

Sucrase: Range 54.4 +/- 25.4
Abnormal <25.0
Disaccharidase Panel

Reference Values:

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Units = uM/min/gram protein data from normal patients

ADICI

Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile Interpretation

Clinical Information: Disseminated intravascular coagulation (DIC) is a consumptive hemorrhagic and microthrombotic disorder that manifests as clinical bleeding or thrombosis. Conditions associated with DIC/ICF can include: sepsis, trauma (head injury, severe tissue injury), obstetric complications (amniotic fluid embolism, abruptio placentae), malignancies, vascular disorders (hemangiomas, aortic aneurysm), and immunologic disorders. These disorders can cause formation of fibrin and fibrin intravascularly, which can result in widespread fibrin deposition contributing to thrombosis and organ failure or, conversely, can result in bleeding due to consumption of coagulation proteins and platelets. DIC/ICF is not a disease; rather it is a syndrome that is secondary to an underlying disorder.

Useful For: Establishing laboratory evidence of disseminated intravascular coagulation (DIC)

Interpretation: An interpretive report will be provided.

Reference Values: Only orderable as part of a profile. For more information see ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma.

**Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma**

**Clinical Information:** Disseminated intravascular coagulation (DIC) and intravascular coagulation and fibrinolysis (ICF), collectively termed DIC/ICF is a consumptive hemorrhagic and microthrombotic disorder that manifests as clinical bleeding or thrombosis. Conditions associated with DIC/ICF can include; sepsis, trauma (head injury, severe tissue injury), obstetric complications (amniotic fluid embolism, abruptio placentae), malignancies, vascular disorders (hemangiomas, aortic aneurysm), and immunologic disorders. These disorders can cause formation of thrombin and fibrin intravascularly, which can result in widespread fibrin deposition contributing to thrombosis and organ failure or, conversely, can result in bleeding due to consumption of coagulation proteins and platelets. DIC/ICF is not a disease, rather it is a syndrome that is secondary to an underlying disorder.

**Useful For:** Establishing laboratory evidence of disseminated intravascular coagulation (DIC)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report is provided.

**Clinical References:** Boender J: A Diagnostic Approach to Mild Bleeding Disorders Journal of Thrombosis and Haemostasis 2016;14:1507-1516

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**Diuretic Screen, Urine**

**Reference Values:**
Qualitative diuretic screen includes: benzthiazide, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, hydroflumethiazide, and metolazone.

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**DMPK DNA Test (DM1)**

**Clinical Information:** Detects CTG repeat expansions in the muscle protein kinase (DMPK) gene. Typical presentation: Adults may present with a range of symptoms from cataracts to significant muscle wasting, cardiac complications, ptosis and myotonia, infants may present with severe hypotonia, skeletal deformities, developmental delay and mental retardation.

**Reference Values:**
A final report will be attached in MayoAccess.

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**DNA Double-Stranded (dsDNA) Antibodies by Crithidia luciliae IFA, IgG, Serum**

**Clinical Information:** A positive Anti-Nuclear Antibodies (ANA) result usually occurs in a number of autoimmune disorders such as systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), Sjögren’s syndrome (SS), and progressive systemic sclerosis (PSS). However, the incidence of low titer ANA positives increases with age in normal individuals. High titers of autoantibodies directed against dsDNA may decrease with successful therapy and increases in acute recurrence of the disease. Also, dsDNA immune complexes play a role in the pathogenesis of SLE through the deposit of the complexes in the kidney and other tissues. For these reasons, the detection of autoantibodies directed against dsDNA is diagnostically and therapeutically helpful in patients suspected or known to have SLE.

**Useful For:** This assay is useful for evaluating patients with suspected or who have the diagnosis of systemic lupus erythematosus.

**Interpretation:** Negative results are considered normal. A positive result for dsDNA antibodies is
consistent with the diagnosis of SLE.

Reference Values:
Only orderable as reflex. For more information see ADNAR / DNA Double-Stranded (dsDNA) Antibodies with Reflex, IgG, Serum.


ADNAR
63073

DNA Double-Stranded (dsDNA) Antibodies with Reflex, IgG, Serum

Clinical Information: Double-stranded (ds, native) DNA (dsDNA) antibodies of the IgG class are an accepted criterion (American College of Rheumatology) for the diagnosis of systemic lupus erythematosus (SLE). (1-3) dsDNA antibodies are detectable in approximately 85% of patients with untreated SLE, and are rarely detectable in other connective tissue diseases. Weakly positive results caused by low-avidity antibodies to dsDNA are not specific for SLE and can occur in a variety of diseases. Testing for IgG antibodies to dsDNA is indicated in patients who have a positive test for antinuclear antibodies (ANA) along with signs and symptoms that are compatible with the diagnosis of SLE. (2) If the ANA test is negative, there is no reason to test for antibodies to dsDNA. (2) The levels of IgG antibodies to dsDNA in serum are known to fluctuate with disease activity in lupus erythematosus, often increasing prior to an increase in inflammation and decreasing in response to therapy. (1,2) See Connective Tissue Diseases Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients with signs and symptoms consistent with systemic lupus erythematosus (SLE), with additional testing by indirect immunofluorescence to clarify cases of borderline ELISA results.

Interpretation: A positive test result for double-stranded DNA (dsDNA) antibodies is consistent with the diagnosis of systemic lupus erythematosus. A reference range study conducted at the Mayo Clinic demonstrated that, within a cohort of healthy adults (n=120), no individuals between the ages of 18 and 60 (n=78) had detectable anti-dsDNA antibodies. Above the age of 60 (n=42), 11.9% of individuals (n=5) had a borderline result for dsDNA antibodies and 4.8% of individuals (n=2) had a positive result.

Reference Values:
<30.0 IU/mL (negative)
30.0-75.0 IU/mL (borderline)
>75.0 IU/mL (positive)
Negative is considered normal.
Reference values apply to all ages.

**ADNA**

**DNA Double-Stranded Antibodies, IgG, Serum**

**Clinical Information:** Double-stranded (ds, native) DNA (dsDNA) antibodies of the IgG class are an accepted criterion (American College of Rheumatology) for the diagnosis of systemic lupus erythematosus (SLE).(1-3) dsDNA antibodies are detectable in approximately 85% of patients with untreated SLE, and are rarely detectable in other connective tissue diseases. Weakly positive results caused by low-avidity antibodies to dsDNA are not specific for SLE and can occur in a variety of diseases. Testing for IgG antibodies to dsDNA is indicated in patients who have a positive test for antinuclear antibodies (ANA) along with signs and symptoms that are compatible with the diagnosis of SLE. If the ANA test is negative, there is no reason to test for antibodies to dsDNA.(2) The levels of IgG antibodies to dsDNA in serum are known to fluctuate with disease activity in lupus erythematosus, often increasing prior to an increase in inflammation and decreasing in response to therapy.(1,2)

**Useful For:** Evaluating patients with signs and symptoms consistent with systemic lupus erythematosus (SLE) Monitoring patients with documented SLE for flares in disease activity

**Interpretation:** A positive test result for double-stranded DNA (dsDNA) antibodies is consistent with the diagnosis of systemic lupus erythematosus. A reference range study conducted at the Mayo Clinic demonstrated that, within a cohort of healthy adults (n=120), no individuals between the ages of 18 and 60 (n=78) had detectable anti-dsDNA antibodies. Above the age of 60 (n=42), 11.9% of individuals (n=5) had a borderline result for dsDNA antibodies and 4.8% of individuals (n=2) had a positive result.

**Reference Values:**
- <30.0 IU/mL (negative)
- 30.0-75.0 IU/mL (borderline)
- >75.0 IU/mL (positive)

Negative is considered normal. Reference values apply to all ages.


**DNJB9**

**DNAJB9 Immunostain, Technical Component Only**

**Clinical Information:** DNAJB9 (Dnaj [hsp40] homolog, subfamily b, member 9) is a heat shock protein that plays a role in protein folding. Proteomic analysis indicates that the DNAJB9 protein is specifically identified in glomeruli of patients with fibrillary glomerulonephritis (FGN). By immunohistochemistry there is an intense smudgy staining of extracellular glomerular deposits for DNAJB9 in patients with FGN.

**Useful For:** Diagnosis of fibrillary glomerulonephritis

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Dock Yellow (Rumex crispus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 17.5 - 49.9 Very High Positive 5 50.0 - 99.9 Very High Positive 6 > or =100 Very High Positive

Reference Values: <0.35 kU/L

Dog Dander, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to dog dander Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

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<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Dog Fennel (Anthemis cotula) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 Positive 4 17.50 - 49.99 Strong Positive 5 50.00 - 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

DOG-1 Immunostain, Technical Component Only

**Clinical Information:** DOG-1 (discovered on gastrointestinal stromal tumors: GIST) is a calcium-regulated chloride channel protein that is expressed strongly on the cell surface of GIST and rarely in other soft tissue tumors, such as uterine type retroperitoneal leiomyomas, peritoneal leiomyomatosis, and synovial sarcomas. DOG-1 may aid in the differential diagnosis of GIST, including KIT-negative and PDGFRA-altered GIST cases.

**Useful For:** Identification of gastrointestinal stromal tumors

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Donath Landsteiner

**Reference Values:** Negative

Douglas Fir, IgE, Serum

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

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

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

**Reference Values:**

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<th>Class</th>
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<tbody>
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<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Doxepin and Nordoxepin, Serum**

**Clinical Information:** Doxepin is recommended for the treatment of psychoneurotic patients with depression or anxiety, or with depression or anxiety associated with alcoholism or organic disease. Nordoxepin (N-desmethyldoxepin) is the major metabolite and is usually present at concentrations equal to doxepin. Optimal efficacy occurs at combined serum concentrations between 50 and 150 ng/mL. Like other tricyclic antidepressants, the major toxicity of doxepin is expressed as cardiac dysrhythmias, which occur at concentrations in excess of 500 ng/mL. Other side effects include nausea, hypotension, and dry mouth.

**Useful For:** Monitoring doxepin therapy Evaluating potential doxepin toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to doxepin when combined serum levels of doxepin and nordoxepin are between 50 and 150 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels are above 500 ng/mL. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

**Reference Values:** Therapeutic concentration (doxepin + nordoxepin): 50-150 ng/mL Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.
Drug Abuse Panel with Confirmation, Chain of Custody, Random, Urine

Clinical Information: This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS), gas chromatography-flame ionization detection (GC-FID), or liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the following drugs:
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Ethanol
- Opiates
- Phencyclidine
- Tetrahydrocannabinol

Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, marijuana, opiates, and phencyclidine. This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (e.g., AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html.

Reference Values:
Negative Screening cutoff concentrations
- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 100 ng/mL
- Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
- Ethanol: 10 mg/dL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

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

Clinical Information: This assay was designed to screen and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the following drugs: 
- Amphetamines 
- Cocaine 
- Opiates 
- Phencyclidine 
- Tetrahydrocannabinol

Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detecting drug abuse involving amphetamines, cocaine, marijuana, opiates, and phencyclidine. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

Reference Values:
Negative
Screening cutoff concentrations
- Amphetamines: 500 ng/mL
- Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

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

Clinical References:

Drug Abuse Survey with Confirmation, Panel 5, Random, Urine

Clinical Information: This assay was designed to screen by immunoassay and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the following drugs: 
- Amphetamines 
- Cocaine 
- Opiates 
- Phencyclidine 
- Tetrahydrocannabinol

This assay represents the coupling of an immunoassay screen with an automatic confirmation of all positive results by the definitive assay available and described in each individual reflex test (eg, AMPHU / Amphetamines Confirmation, Urine). All positive screening results are confirmed by GC-MS or LC-MS/MS, and quantitated, before a positive result is reported.

Useful For: Detecting drug abuse involving amphetamines, cocaine, marijuana, opiates, and phencyclidine. This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html

Reference Values:
Negative
Screening cutoff concentrations
- Amphetamines: 500 ng/mL
- Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


CDA7X 62716

Drug Abuse Survey with Confirmation, Panel 9, Chain of Custody, Random, Urine

Clinical Information: This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the most common classes of drugs of abuse. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS (positive alcohol by GC) or LC-MS/MS and quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html.

Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylcgonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Drug Abuse Survey with Confirmation, Panel 9, Random, Urine

Clinical Information: This assay was designed to screen by immunoassay and confirm by gas chromatography-mass spectrometry (GC-MS), gas chromatography-flame ionization detection (GC-FID), or liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the following drugs:
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Ethanol
- Opiates
- Methadone
- Phencyclidine
- Tetrahydrocannabinol

This test represents the coupling of an immunoassay screen with an automatic confirmation of all positive results by the definitive assay available and described in each individual reflex test (eg, AMPHU / Amphetamines Confirmation, Urine). All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS and quantitated before a positive result is reported.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol.

This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html

Reference Values:

Negative
Screening cutoff concentrations
- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 100 ng/mL
- Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
- Ethanol: 10 mg/dL
- Methadone metabolite: 300 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

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

Reference Values:
Negative
Screening cutoff concentrations
- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 100 ng/mL
- Cocaine (benzylecgonine-cocaine metabolite): 150 ng/mL
- Ethanol: 10 mg/dL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

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


PNRCH 65061

Drug Immunoassay Panel, Urine

Clinical Information: This test uses the simple screening technique that involves immunologic testing for drugs by class. All positive immunoassay screening results are confirmed by gas chromatography-mass spectrometry (GC-MS) and quantitated before a positive result is reported. This assay was designed to test for and confirm by GC-MS the following: - Barbiturates - Cocaine - Tetrahydrocannabinol This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving barbiturates, cocaine, and tetrahydrocannabinol

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. See individual tests (eg, COKEU / Cocaine and Metabolite Confirmation, Random, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html

Reference Values:
Only orderable as part of profile. For more information see CSMPU / Controlled Substance Monitoring Panel, Random, Urine.

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

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

Drug Screen, Prescription/Over the Counter, Chain of Custody, Random, Urine

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opiates. For these drugs, see Mayo Clinic Laboratories' drug abuse surveys, drug screens, or individual tests. Chain of custody is a record of the disposition of a specimen to document the personnel who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions for detection limits for drugs detected in this test.

Useful For: The qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent Providing, when possible, the identification of all drugs present This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. This test is not useful for the assessment of therapeutic compliance. This test is not intended for use in employment-related testing. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The drugs that can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, request a Clinical and Forensic Toxicology Lab consult (Mayo Clinic patients) or contact Mayo Laboratory Inquiry (Mayo Clinic Laboratories clients).

Reference Values:
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.


Drug Screen, Prescription/Over the Counter, Chain of Custody, Serum

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids,
barbiturates, cocaine, and amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and most opiates. See Prescription and Over-the-Counter (OTC) Drug Screens Table 1 in Special Instructions for detection limits for drugs detected in this test.

**Useful For:** Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent. Qualitatively identifying drugs present in the specimen; quantification of identified drugs, when available, may be performed upon client request. This test is not intended for therapeutic drug monitoring or compliance testing. This test is not intended for use in employment-related testing. This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The drugs that are detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens Table 1 in Special Instructions. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If you wish to have a report interpreted, call 800-533-1710 and ask for a toxicology consultant. Each report will indicate the drugs detected.

**Reference Values:**

Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

**Clinical References:**


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**Drug Screen, Prescription/Over the Counter, Random, Urine**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, salicylate and many drugs of abuse or illicit drugs, some benzodiazepines, and some opioids. For these drugs, see Mayo Clinic Laboratories' drug abuse surveys, drug screens, or individual tests. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions for detection limits for drugs detected in this test.

**Useful For:** Qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent. Providing, when possible, the identification of all drugs present in the specimen. This test is not intended for use in employment-related testing. This test is not intended for therapeutic compliance testing. This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants.

**Interpretation:** The drugs that can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, request a Clinical and Forensic Toxicology Lab consult (Mayo Clinic patients) or contact Mayo Laboratory Inquiry (Mayo Clinic Laboratories clients).

**Reference Values:**
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.


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**DSS 8421**

**Drug Screen, Prescription/Over the Counter, Serum**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opioids. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions for detection limits for drugs detected in this test.

**Useful For:** Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent Qualitatively identifying drugs present in the specimen; quantification of identified drugs, when available, may be performed upon client request This test is not intended for therapeutic drug monitoring or compliance testing. This test is not intended for use in employment-related testing. This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, amphetamine type stimulants.

**Interpretation:** The drugs that are detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If you wish to have a report interpreted, call 800-533-1710 and ask for a toxicology consultant. Each report will indicate the drugs detected.

**Reference Values:**

Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.


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**FDA1S 75525**

**Drugs of Abuse (10 panel) and Alcohol Screen, Serum**

**Reference Values:**

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<td>Cocaine/Metabolites</td>
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<td>Amphetamines</td>
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<td>ng/mL</td>
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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Drugs of Abuse Screen (10 panel), Serum

Reference Values:

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<td>Benzodiazepines</td>
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</tr>
<tr>
<td>Cannabinoids</td>
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<td>ng/mL</td>
</tr>
<tr>
<td>Amphetamines</td>
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<td>ng/mL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Methadone/Metabolite</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Methamphetamine/MDMA</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Oxycodone/Oxymorphone</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
</tbody>
</table>

Drugs of Abuse Screen 4, Chain of Custody, Meconium

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. (1) In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, drug withdrawal) are increased. (1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. (2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. (3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis. (2) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimen. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.
Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**

- Amphetamines by ELISA: 100 ng/g
- Methamphetamine by ELISA: 100 ng/g
- Benzoylecgonine (cocaine metabolite) by ELISA: 100 ng/g
- Opiates by ELISA: 100 ng/g
- Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g

**Clinical References:**

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**DSM5X 62722**

**Drugs of Abuse Screen 5, Chain of Custody, Meconium**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by uranalysis. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g -Phencyclidine (PCP): >20 ng/g

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.
Drugs of Abuse Screen, Meconium 4

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. (1) In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, drug withdrawal) are increased. (1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. (2) The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. (3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. (2)

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens

**Interpretation:** A positive result indicates that the baby was exposed to the drugs indicated.

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - Amphetamines by ELISA: 100 ng/g
  - Methamphetamine by ELISA: 100 ng/g
  - Benzoylecgonine (cocaine metabolite) by ELISA: 100 ng/g
  - Opiates by ELISA: 100 ng/g
  - Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g

incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

Useful For: Identifying amphetamines (and methamphetamines), opiates, phencyclidine (PCP), as well as metabolites of cocaine and marijuana in meconium specimens

Interpretation: A positive result indicates that the baby was exposed to the drugs indicated.

Reference Values:
Positive results are reported with a quantitative LC-MS/MS result.

Cutoff concentrations:
- Amphetamines by ELISA: 100 ng/g
- Methamphetamine by ELISA: 100 ng/g
- Benzoylecgonine (cocaaine metabolite) by ELISA: 100 ng/g
- Opiates by ELISA: 100 ng/g
- Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g
- Phencyclidine by ELISA: 20 ng/g

Clinical References:

Duchenne/Becker Muscular Dystrophy, DMD Gene, Large Deletion/Duplication Analysis, Varies

Clinical Information: Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder characterized initially by proximal muscle weakness beginning before age 5 years. Affected individuals typically have pseudohypertrophy of the calf muscles and exhibit toe-walking, waddling gait, and the Gower sign (climbing up the legs when rising from a seated position on the floor). Not only is skeletal muscle affected in DMD, but also the smooth muscle of the gastrointestinal tract and possibly bladder, as well as cardiac muscle. Initial symptoms are followed by dramatic progression of weakness leading to loss of ambulation by age 11 or 12. Death is often caused by cardiac failure or by respiratory failure before age 30, unless ventilator support is provided. The allelic Becker muscular dystrophy (BMD) has a similar presentation, although age of onset is later and the clinical course is much milder. Cardiac involvement can be the only sign and patients are often ambulatory into their thirties. DMD and BMD are caused by mutations in the DMD gene, which encodes for dystrophin. Approximately 50% to 65% of patients have intragenic deletions and approximately 5% to 10% have intragenic duplications. Less frequently, DMD and BMD result from nondeletion and nonduplication mutations, which are not detected by this assay. Approximately one-third of sporadic cases of DMD/BMD occur due to new mutations. In sporadic cases, it is possible for the mother of an affected individual to have germline mosaicism. This means that the germ cells may contain a mutation even if the mutation is not detected in peripheral blood. In cases of germine mosaicism, which occurs with a frequency of up to 15%, further offspring are at risk for inheriting a dystrophin mutation.

Useful For: Confirmation of a clinical diagnosis of Duchenne muscular dystrophy (DMD) or Becker
muscular dystrophy (BMD) Distinguishing DMD from BMD in some cases, based on the type of deletion detected (allows for better prediction of prognosis) Determination of carrier status in family member at risk for DMD or BMD Prenatal diagnosis of DMD or BMD in at-risk pregnancies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**DUCK**

**Duck Feathers, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to duck feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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<td>Negative</td>
</tr>
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<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
</tbody>
</table>
| 6             | > or =100      | Strongly positive Reference values apply to all ages.

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry’s Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
**Duck Meat IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Duloxetine, Serum**

**Clinical Information:** Duloxetine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class. It is effective in treating symptoms of depression, including physical pain associated with depression; other uses include therapy of neuropathic pain, fibromyalgia, and urinary stress incontinence. Duloxetine also inhibits serotonin uptake in human platelets and may be associated with potentiation of bleeding. Duloxetine undergoes extensive hepatic biotransformation to numerous inactive metabolites. The drug is metabolized by cytochrome P450 (CYP) 1A2 and CYP2D6, with moderate potential for drug interactions (duloxetine is both a substrate and a moderate inhibitor of CYP2D6). The mean elimination half-life is 12.5 hours with steady-state concentrations occurring in about 3 days. Specimens for therapeutic monitoring should be collected immediately before the next scheduled dose (ie, trough). Duloxetine is not recommended for patients with hepatic impairment, substantial alcohol use, or chronic liver disease. Use in patients with renal disease significantly increases exposure to duloxetine due to decreased elimination. Patients with mild-to-moderate renal dysfunction should be monitored closely; use of duloxetine is not recommended in end-stage renal disease.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity Evaluating patient compliance

**Interpretation:** Therapeutic ranges are not well-established, but literature suggests that patients receiving duloxetine monotherapy for depression responded well when trough concentrations were 30 to 120 ng/mL. Higher levels may be tolerated by individual patients. The therapeutic relevance of this concentration range to other uses of duloxetine therapy is currently unknown.

**Reference Values:**
30-120 ng/mL

**Clinical References:**

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**E-Cadherin Immunostain, Bone Marrow, Technical Component**

**Clinical Information:** Membrane protein expressed on normal breast epithelial cells. Expression can
be lost on lobular neoplasms of the breast, in contrast to ductal neoplasms of the breast.

**Useful For:** Differentiation between lobular and ductal neoplasms of the breast

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**ECAD 70423**

**E-Cadherin Immunostain, Technical Component Only**

**Clinical Information:** Membrane protein expressed on normal breast epithelial cells. Expression can be lost on lobular neoplasms of the breast, in contrast to ductal neoplasms of the breast.

**Useful For:** Differentiation between lobular and ductal neoplasms of the breast

**Interpretation:** This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**EEPC 83917**

**Eastern Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid**

**Clinical Information:** Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low-prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70% EEE. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod, relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.
**Useful For:** Aiding in the diagnosis of Eastern equine encephalitis

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>&lt;1:1</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;1:1</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:**

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**Eastern Equine Encephalitis Antibody, IgG and IgM, Serum**

**Clinical Information:** Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals; it is more abrupt and more severe with EEE than other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70% for EEE.

**Useful For:** Aiding in the diagnosis of Eastern equine encephalitis

**Interpretation:** In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG greater than or equal to 1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity. Infections can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.

**Reference Values:**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>&lt;1:10</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;1:10</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:**
4. Calisher CH: Medically important arboviruses of the United States and Canada. Clin
**ESYC 82721**

**Eastern Sycamore, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Eastern Sycamore Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<th>Class</th>
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<th>Interpretation</th>
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<td>0.35-0.69</td>
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<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**ECHNO 64985**

**Echinococcus Antibody, IgG, Serum**

**Clinical Information:** Echinococcosis, also referred to as hydatidosis or hydatid disease, is 1 of the 17 neglected tropical diseases recognized by the World Health Organization and affects over 1 million people worldwide. Echinococcus species are tapeworms or cestodes, and 2 main species infect humans: Echinococcus granulosus and Echinococcus multilocularis. With respect to geographic distribution, E granulosus can be found worldwide, more frequently, is found in rural grazing areas where dogs may feed on infected sheep or cattle carcasses. E multilocularis is largely localized to the northern
hemisphere. The definitive hosts for E granulosus are dogs or other canids, while the definitive host for 
E multilocularis are foxes and, to a much lesser extent, canids. Echinococcus tapeworms reside in the 
small intestine of definitive hosts and release eggs that are passed in the feces and ingested by an 
intermediate host, typically sheep or cattle in the case of E granulosus or small rodents for E 
multilocularis. The eggs hatch in the small bowel, releasing an oncosphere that penetrates the intestinal 
wall and migrates through the circulatory system to various organs where it develops into a cyst that 
gradually enlarges producing protoscolicities and daughter cysts, which fill the interior. The definitive 
host becomes infected following ingestion of these infectious cysts. Humans become accidentally 
infected following ingestion of Echinococcus eggs. In humans, E granulosus (cystic echinococcal 
disease) cysts typically develop in the lungs and liver, and the infection may remain silent or latent for 
years (5-20 years) prior to cyst enlargement and symptom manifestation. Symptomatic manifestations 
include chest pain, hemoptysis, and cough for pulmonary involvement and abdominal pain and biliary 
duct obstruction for liver infection. E multilocularis (alveolar echinococcal disease) infections manifest 
more rapidly than those of E granulosus and similarly to a rapidly growing, destructive tumor, resulting 
in abdominal pain and biliary obstruction. Rupture of cysts can produce fever, urticaria, and 
anaphylactic shock. Diagnosis of echinococcal infections relies on characteristic finding by ultrasound 
or other imaging techniques and serologic findings. Fine-needle aspirates of cystic fluid may be 
performed; however, they carry the risk of cyst puncture and fluid leakage, which may potentially lead 
to severe allergic reactions. Importantly, infected individuals do not shed eggs in stool.

Useful For: Detection of antibodies to Echinococcus species, including Echinococcus multilocularis 
and Echinococcus granulosus

Interpretation: Negative: The absence of antibodies to Echinococcus species suggests that the 
individual has not been exposed to this cestode. A single negative result should not be used to rule-out 
infection (see Cautions). Equivocal: Consider repeat testing on a new serum sample in 1 to 2 weeks. 
Positive: Results suggest infection with Echinococcus. False-positive results may occur in settings of 
infection with other helminths, or in patients with chronic immune disorders. Results should be 
considered alongside other clinical findings (eg, characteristic findings on imaging) and exposure history.

Reference Values:
Negative
Reference values apply to all ages.


Eculizumab Monitoring Panel, Serum

Clinical Information: Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized hybrid 
monoclonal antibody (IgG2/IgG4) that blocks complement C5 cleavage, thereby preventing the activation 
of the proinflammatory effects of C5a and the cytolytic effects of the membrane attack complex (MAC) 
formed by C5b-C9. It is FDA-approved for atypical hemolytic uremic syndrome(1) and paroxysmal 
nighturnal hemoglobinuria,(2) and it is also prescribed for other conditions such as C3 
glomerulopathies.(3) The dosing regimen for an average adult may vary from 300 to 1,200 mg 
intravenously every 2 weeks during the maintenance stages, according to the condition for which the drug 
is prescribed. Therapy efficacy may be monitored by measuring efficiency of complement blockade.(4) 
Eculizumab will affect complement function assays that rely on the formation of the MAC to generate cell 
lysis. Although total complement (CH50) and soluble membrane attack complex (sMAC) have been 
recommended for eculizumab monitoring, the measurement of C5 function and C5 antigen more 
specifically indicate the impact of eculizumab on the complement system blockage and may help guide 
the next dose of the drug. This panel measures the pharmacodynamics effects of eculizumab on the 
complement system.

Useful For: Therapeutic drug monitoring of eculizumab

Interpretation: The panel will measure the pharmacodynamic effects of eculizumab on the
complement system. Total complement (CH50) function, alternative pathway (AH50) function, and C5 function assays will be decreased to a similar extent in the presence of eculizumab. The function of C5 may be completely absent when eculizumab is present at therapeutic concentrations. C5 antigen, on the other hand, will be normal or elevated. C5 complement function drops on average 30% with 25 mcg/mL of eculizumab, and 70% with 50 mcg/mL. In the presence of 100 mcg/mL of eculizumab in serum, there is on average 20% residual C5 function. Decreased C5 function in the presence of normal or elevated C5 antigen concentrations suggests eculizumab is partially blocking C5 activity. Absent C5 function in the presence of normal or elevated C5 antigen concentrations suggests eculizumab is completely blocking C5 activity. Normal C5 function in the presence of normal or elevated C5 antigen concentrations suggests eculizumab concentration is not sufficient to block C5 activity. If C5 function and C5 antigen concentrations are all decreased, it may be due to a secondary consumption process, poor hepatic synthesis of complement proteins or C5 deficiency. Clinical correlation recommended. If indicated, resubmit samples to confirm results.

**Reference Values:**

- **C5 COMPLEMENT ANTIGEN**
  - 10.6-26.3 mg/dL

- **C5 COMPLEMENT FUNCTIONAL**
  - 29-53 U/mL

**Clinical References:**


**ECULIZUMAB, Serum**

**Clinical Information:**

Eculizumab (Soliris, Alexion Pharmaceuticals), a humanized monoclonal IgG2/4 kappa antibody therapeutic directed against complement component C5, has been heralded as a breakthrough treatment for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). By association with C5, eculizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Since all 3 arms of the complement cascade converge at the point of C5 activation, targeted by eculizumab, this drug may have broad potential application and is being clinically evaluated in other disorders with complement overactivation. In PNH, eculizumab has become the standard of care, proving to be a safe and effective therapy with long-lasting effects, potentially enabling patients to become transfusion-independent and extending their survival. Eculizumab is administered as an IV infusion, and the dosing regimen prescribed for an average adult diagnosed with PNH is 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later; then, 900 mg every 2 weeks thereafter. Eculizumab has been evaluated in aHUS patients through 2 prospective, open-label, single-arm studies (C08-002 and C08-003) as well as a single-arm retrospective study. In aHUS, it is prescribed for an average adult at 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Eculizumab was generally well tolerated and no significant adverse effects were attributed to drug treatment; some adverse reactions included upper respiratory tract infections and diarrhea in prospective and retrospective studies, hypertension, headache, and leukopenia (C08-002/C08-003), and fever (C09-001R). Additional case reports suggest that eculizumab may prevent posttransplantation recurrence of aHUS, even in those patients harboring CFH/CFHR1 hybrid gene variants, who are at very high risk of recurrence. Further research is needed to determine the duration of eculizumab therapy in the context of the genetic background of aHUS cases and risk of disease relapse. The drawbacks of eculizumab therapy are associated with its potentially life-threatening
side-effects, variations in response profiles, and the cost of treatment. Patients treated with eculizumab are at an increased risk of susceptibility towards life-threatening infections such as Neisseria meningitides; to prevent such infections, vaccinations and, in some cases, prophylactic antibiotic treatment is recommended. A number of serious and potentially treatment-related adverse effects were observed including pyrexia, headache, abdominal distension, viral infection, renal impairment, and anxiety. It is important to note that there is variability among individuals towards eculizumab response, and some patients may not benefit from this therapy. This is potentially a life-long therapy with a high cost of administration. The cost of eculizumab may limit its use in routine clinical practice worldwide. Therapeutic drug monitoring of eculizumab is typically not performed during treatment regimens due to the low toxicity of biologics. Measurement of therapy efficacy is usually based on clinical presentation and improvement of symptoms, although this landscape is changing, as it is recognized that patients undergoing life-long therapy with eculizumab who are in complete remission without significant evidence or pathogenic genetic variants leading to increased risk of relapse may benefit from dose de-escalation or discontinuing therapy. Pharmacodynamic studies of complement blockage may also be recommended, see ECUMP / Eculizumab Monitoring Panel, Serum for more information.

**Useful For:**
- Assessing the response to eculizumab therapy
- Assessing the need for dose escalation
- Evaluating the potential for dose de-escalation or discontinuation of therapy in remission states
- Monitoring patients who need to be above a certain eculizumab concentration in order to improve the odds of a clinical response for therapy optimization

**Interpretation:** Minimum trough therapeutic concentrations (immediately before next infusion) of eculizumab are expected to be above 35 mcg/mL for paroxysmal nocturnal hemoglobinuria (PNH) and above 50 mcg/mL for aHUS.

**Reference Values:**
- Lower limit of quantitation =5.0 mcg/mL
- >35 Therapeutic concentration for paroxysmal nocturnal hemoglobinuria (PNH)
- >50 Therapeutic concentration for atypical hemolytic uremic syndrome (aHUS)

**Clinical References:**

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**EDOXA**

**EDOXA 606009**

**E Doxaban, Anti-Xa, Plasma**

**Clinical Information:** Edoxaban, an oral anticoagulant that directly inhibits factor Xa, has been approved by the FDA for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the treatment of venous thromboembolism (VTE). Unlike warfarin, it does not require routine therapeutic monitoring. However, in selected clinical situations, measurement of drug level would be useful (eg, renal insufficiency, assessment of compliance, peri-procedural measurement of drug concentration, suspected overdose, advanced age and extremes of body weight). Predicted Edoxaban Steady-State Exposure Concentrations Nonvalvular atrial fibrillation (1) Median trough levels* (24 hours after last dose) Median peak levels (2 hours after dose) 30 mg once daily 38 ng/mL (7-147) 169 ng/mL (10-400) 60 mg once daily 39 ng/mL (13-110) 300 ng/mL (60-569) Nonvalvular atrial fibrillation (2) Median trough levels* (median collection time 20 hours (IQR 15.4-24.3) post dose) 30 mg once daily 18.4 ng/mL (10.1-32.3) 60 mg once daily 36 ng/mL (19-62) Deep vein thromboembolism and pulmonary embolism continued treatment (3) Median trough levels (obtained pre-dose) Peak levels (obtained 1-3 hours post dose) 30 mg once daily 16 ng/mL (IQR 8.3-32) 164 ng/mL (IQR 99-225) 60 mg once daily 19 ng/mL (10-39) 234 ng/mL (IQR 149-317) *Trough levels derived from separate references/studies containing different post dose draw times.

**Useful For:** Measuring edoxaban concentration in plasma This test is not useful for monitoring...
low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) concentrations.

**Interpretation:** The lower limit of detection of this assay is 10 ng/mL. Therapeutic reference ranges have not been established. For peak and trough drug concentrations observed from clinical trials see Clinical Information.

**Reference Values:**
<10 ng/mL


**EGFR Exon 18, 19, 20, 21, Mutation Analysis, Cell-Free DNA, Plasma**

**Clinical Information:** Approximately 25% of non-small cell lung cancers (NSCLC) have mutations in the EGFR gene. Most mutations occur in hotspot regions in exons 18, 19, 20 and 21. EGFR is activated by the binding of specific ligands, resulting in activation of the RAS/mitogen-activated protein kinase (MAPK) pathway. EGFR-targeted therapies (eg, gefitinib and erlotinib) have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to traditional chemotherapy. Current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I, or small deletions within exon 19 and the absence of drug-resistant mutations (eg, exon 20 insertions and T790M). As a result, the mutation status of EGFR is a critical marker for selecting patients for EGFR-targeted therapy. This FDA approved test uses DNA extracted from the peripheral blood to evaluate for the presence of mutations in exons 18, 19, 20, and 21 of the EGFR gene. A positive result indicates the presence of an EGFR mutation and may be useful for guiding the treatment of individuals with non-small cell lung cancer. At this time, this test is approved specifically for patients with lung cancer. The utilization of this test in patients with other tumor types could be considered an off-label use of this test.

**Useful For:** As an alternative to invasive tissue biopsies for the determination of EGFR-mutation status Selection of patients with non-small cell lung cancer who are most likely to benefit from targeted therapies

**Interpretation:** An interpretive report will be provided.

EGFR Gene, Mutation Analysis, 29 Mutation Panel, Tumor

Clinical Information: Lung cancer is the leading cause of cancer-related deaths in the world. Non-small cell lung cancer (NSCLC) represents 70% to 85% of all lung cancer diagnoses. Small molecular agents that target the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) protein are approved for the treatment of locally advanced or metastatic NSCLC as a second- or third-line regimen. Subsequently, randomized trials have suggested that targeted agents alone or combined with chemotherapy may be beneficial in maintenance and first-line settings. Because the combination of targeted therapy and standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from targeted therapies are desirable. EGFR is a growth factor receptor that is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression for many solid tumors. Targeted therapies directed to tumors harboring activating mutations within the EGFR tyrosine kinase domain (exons 18-21) have demonstrated some success in treating a subset of patients with NSCLC by preventing adenosine 5'-triphosphate (ATP)-binding at the active site. Gefitinib and erlotinib have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to the traditional platinum-based doublet chemotherapy. These 2 drugs have also recently been shown to increase progression-free and overall survival in patients who receive EGFR-tyrosine kinase inhibitor therapy as a first-line therapy for the treatment of NSCLC. Agents such as gefitinib and erlotinib, which prevent ATP binding to EGFR kinase, do not appear to have any meaningful inhibitor activity on tumors that demonstrate the presence of the specific drug-resistant EGFR mutation T790M. Therefore, current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I or small deletions within exon 19 and the absence of the drug-resistant mutation T790M. As a result, the mutation status of EGFR can be a useful marker by which patients are selected for EGFR-targeted therapy.

Useful For: Identifying non-small cell lung cancers that may respond to epidermal growth factor receptor-tyrosine kinase inhibitor therapies

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


Egg White IgG

Interpretation:

Reference Values: Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Egg White IgG4

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Egg White, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to egg white Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Egg Whole IgG**

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

**Egg Yolk IgG**

**Interpretation:**

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

**Egg Yolk, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to egg yolk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
</tbody>
</table>

Eggplant, IgE, Serum

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

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

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

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<th>IgE kU/L</th>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Ehlers-Danlos Syndrome Panel (12 Genes), Next-Generation Sequencing and Deletion/Duplication Analysis, Varies

Clinical Information: The Ehlers Danlos syndromes (EDS) are a clinically and genetically diverse group of heritable connective tissue disorders. An EDS classification system proposed by the International EDS Consortium identifies 13 subtypes of EDS, with an overall estimated prevalence of EDS between 1:5,000 and 1:25,000. Over 90% of cases are either classic or hypermobile EDS (cEDS or hEDS), while less than 5% of cases are vascular EDS (vEDS). Other, rarer, subtypes of EDS also exist and are listed in the table below. The clinical hallmarks of EDS are joint hypermobility, skin hyperextensibility, and tissue fragility. However, a variety of skin, ligament, joint, and cardiovascular features are seen across the spectrum of EDS. A clinical diagnosis of a specific subtype of EDS may be suspected based on a combination of major (a symptom present in the majority of affected individuals) and minor (a symptom of lesser diagnostic specificity that supports the diagnosis) clinical criteria. However, due to the clinical overlap between EDS subtypes and other heritable connective tissue disorders (eg, Marfan syndrome and Loeys-Dietz syndrome), a definitive diagnosis of all EDS subtypes (except EDS hypermobility type) relies on the identification of a causative variant in the appropriate gene. Genetic variants in collagen-encoding or collagen-modifying genes have been identified as the cause of EDS in the majority of subtypes. These variants result in defects in collagen structure, processing, folding and cross-linking. One notable exception to this is hypermobile EDS (hEDS). Hypermobile EDS is inherited in an autosomal dominant inheritance pattern, similar to cEDS and vEDS, however, the molecular basis of this condition is unknown and a diagnosis is based on clinical criteria. This panel also tests for variants in the ATP7A and FLNA genes, which result in X-linked conditions. Some patients with these conditions have clinical overlap with EDS. Table 1. Genes included in the EDS Gene Panel.

<table>
<thead>
<tr>
<th>GENE SYMBOL (ALIAS)</th>
<th>PROTEIN</th>
<th>INHERITANCE*</th>
<th>EDS CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS2</td>
<td>Procollagen I N-proteinase (NPI)</td>
<td>AR</td>
<td>Dermatosparaxis EDS (dEDS) / human dermatosparaxis EDS</td>
</tr>
<tr>
<td>ATP7A</td>
<td>Copper-transporting ATPase 1</td>
<td>XL</td>
<td>Occipital horn syndrome CHST14 derm &gt; dermatan-4-sulfotransferase-1 (D4ST1)</td>
</tr>
<tr>
<td>CHST14</td>
<td></td>
<td>AR</td>
<td>Musculocontractual EDS (mEDS-CHST14)</td>
</tr>
<tr>
<td>COL1A1</td>
<td>Collagen alpha-1(I) chain AD</td>
<td>AD</td>
<td>EDS VIIC (human dermatosparaxis EDS)</td>
</tr>
<tr>
<td>COL1A2</td>
<td>Collagen alpha-2(I) chain AD</td>
<td>AD</td>
<td>Arthrochalasia EDS (aEDS)</td>
</tr>
<tr>
<td>COL3A1</td>
<td>Collagen alpha-1(III) chain AD</td>
<td>AD</td>
<td>Cardiac valvular EDS (cvEDS)</td>
</tr>
<tr>
<td>COL5A1</td>
<td>Collagen alpha-1(V) chain AD</td>
<td>AD</td>
<td>Vascular EDS (vEDS)</td>
</tr>
<tr>
<td>COL5A2</td>
<td>Collagen alpha-2(V) chain AD</td>
<td>AD</td>
<td>Vascular EDS (vEDS)</td>
</tr>
<tr>
<td>FKBP14</td>
<td>Peptidyl-prolyl cis-trans isomerase</td>
<td>AR</td>
<td>Kyphoscoliotic EDS (kEDS-FKBP14)</td>
</tr>
<tr>
<td>FLNA</td>
<td>Filamin A</td>
<td>XL</td>
<td>Filamin A related EDS</td>
</tr>
<tr>
<td>PLOD1</td>
<td>Procollagen-lysine 5-dioxygenase</td>
<td>AR</td>
<td>Periventricular nodular heterotopia (PLOD1)</td>
</tr>
<tr>
<td>SLC39A13</td>
<td>Zinc transporter</td>
<td>AR</td>
<td>Spondylo dysplastic EDS (spEDS-SLC39A13)</td>
</tr>
</tbody>
</table>

*Abbreviations: Autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), Ehlers-Danlos syndrome (EDS)

Useful For: Confirmation of a clinical diagnosis of Ehlers-Danlos Syndrome (EDS) Differentiating between the different subtypes of EDS for diagnosis and management purposes Ascertaining carrier status of family members of individuals diagnosed with EDS for genetic counseling purposes

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

Ehrlichia Antibody Panel, Serum

Clinical Information: Anaplasma phagocytophilum: Anaplasma phagocytophilum, an intracellular rickettsia-like bacterium, preferentially infects granulocytes and forms inclusion bodies, referred to as morulae. A phagocytophilum is transmitted by Ixodes species ticks, which also transmit Borrelia burgdorferi and Babesia species. Infection with A phagocytophilum is also referred to as human granulocytic anaplasmosis (HGA) and symptoms in otherwise healthy individuals are often mild and nonspecific, including fever, myalgia, arthralgia, and nausea. Clues to the diagnosis of anaplasmosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated liver enzymes. HGA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. Ehrlichia chaffeensis: Ehrlichia chaffeensis is an intracellular rickettsia-like bacterium that preferentially infects monocytes and is sequestered in parasitophorous vacuoles referred to as morulae. Infections with E chaffeensis are also referred to as human monocytophagocytic ehrlichiosis (HME). E chaffeensis is transmitted by Amblyomma species ticks, which are found throughout the southeastern and south central United States. Many cases of HME are subclinical or mild, however, the infection can be severe and life-threatening, particularly in immunosuppressed individuals. Reported mortality rates range from 2% to 3%. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings.

Useful For: An adjunct in the diagnosis of infection with Anaplasma phagocytophilum or Ehrlichia chaffeensis Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive immunofluorescence assay (titer \( \geq 1:64 \)) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection.

Reference Values:
ANAPLASMA PHAGOCYTOPHILUM
<1:64
Reference values apply to all ages.

EHRlichia ChAFFEENIsIS
<1:64
Reference values apply to all ages.

Clinical References: Centers for Disease Control and Prevention (CDC), Division of Vector-Borne Diseases: Tickborne diseases of the United States: A Reference manual for health care providers. 4th ed. CDC; 2017

Ehrlichia chaffeensis (HME) Antibody, IgG, Serum

Clinical Information: Ehrlichia chaffeensis is an intracellular rickettsia-like bacterium that preferentially infects monocytes and is sequestered in parasitophorous vacuoles referred to as morulae. Infections with E chaffeensis are also referred to as human monocytophagocytic ehrlichiosis (HME). E chaffeensis is transmitted by Amblyomma species ticks, which are found throughout the southeastern and south central United States. Many cases of HME are subclinical or mild, however, the infection can be severe and life-threatening, particularly in immunosuppressed individuals. Reported mortality rates range from 2% to 3%. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory
Useful For: An adjunct in the diagnosis of ehrlichiosis Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive immunofluorescence assay (titer \( \geq 1:64 \)) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection.

Reference Values:
<1:64
Reference values apply to all ages.

Clinical References: Centers for Disease Control and Prevention (CDC), Division of Vector-Borne Diseases: Tickborne diseases of the United States: A Reference manual for health care providers. 4th ed. CDC; 2017

Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood

Clinical Information: Ehrlichiosis and anaplasmosis are a group of emerging zoonotic tick-borne infections caused by Ehrlichia and Anaplasma species, respectively. These obligate intracellular, gram-negative rickettsial organisms infect leukocytes and cause a potentially serious febrile illness in humans. Human granulocytic anaplasmosis (HA) is caused by Anaplasma phagocytophilum, which is transmitted through the bite of an infected Ixodes species tick. The epidemiology of this infection in the United States is very much like that of Lyme disease (caused by Borrelia burgdorferi) and babesiosis (caused primarily by Babesia microti), which all have the same tick vector. HA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. Human monocytic ehrlichiosis (HE) is caused by Ehrlichia chaffeensis, which is transmitted by the Lone Star tick, Amblyomma americanum. Most cases of HE have been reported from the southeastern and south-central regions of the United States. E ewingii, the known cause of canine granulocytic ehrlichiosis, can occasionally cause an HE-like illness in humans. Clinical features and laboratory abnormalities are similar to those of E chaffeensis infection, and antibodies to E ewingii cross-react with current serologic assays for detection of antibodies to E chaffeensis. Most recently, Mayo Clinic Laboratories detected a new species of Ehrlichia in patients with exposure to ticks in Wisconsin and Minnesota. This organism is most closely related to E muris and has therefore been referred to as the E muris-like agent or EMLA. The name E muris eauclairensis has recently been proposed after the city in which the first case was described. E muris eauclairensis causes a similar disease to ehrlichiosis due to E chaffeensis and E ewingii, and may cause more severe disease in immunocompromised hosts. Most cases of anaplasmosis and ehrlichiosis are subclinical or mild, but infection can be severe and life-threatening in some individuals. Fever, fatigue, malaise, headache, and other “flu-like” symptoms, including myalgias, arthralgias, and nausea, occur most commonly. Central nervous system involvement can result in seizures and coma. Diagnosis may be difficult since the patient’s clinical course is often mild and nonspecific. This symptom complex is easily confused with other illnesses such as influenza, or other tick-borne zoonoses such as Lyme disease, babesiosis, and Rocky Mountain spotted fever. Clues to the diagnosis of ehrlichiosis in an acutely febrile patient after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated serum aminotransferase levels. However, while these abnormal laboratory findings are frequently seen, they are not specific. Rarely, intra-granulocytic or monocytic morulae may be observed on peripheral blood smear, but this is not a reliable means of diagnosing cases of human ehrlichiosis or anaplasmosis. Definitive diagnosis is usually accomplished through PCR and serologic methods. Serologic testing is done primarily for confirmatory purposes, by demonstrating a 4-fold rise or fall in specific antibody titers to Ehrlichia species or Anaplasma antigens. There is not currently a commercially available specific serologic test for E muris eauclairensis, but cross-reactivity with the other Ehrlichia species by serology may be detected. PCR techniques allow direct detection of pathogen-specific DNA from patients’ whole blood and is the preferred method for detection during the acute phase of illness. The Mayo PCR assay is capable of detecting and differentiating A phagocytophilum, E chaffeensis, E ewingii, and E muris eauclairensis. It is important to note that concurrent infection with A phagocytophilum, Borrelia burgdorferi, and Babesia microti is not uncommon as these organisms share the same Ixodes tick vector.
and additional testing for these pathogens may be indicated.

**Useful For:** Evaluating patients suspected of acute anaplasmosis or ehrlichiosis

**Interpretation:** Positive results indicate presence of specific DNA from *Ehrlichia chaffeensis*, *E ewingii*, *E muris eauclairensis* organism, or *Anaplasma phagocytophilum* and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens, but do not exclude the presence of these organisms or active or recent disease. Since DNA of *E ewingii* is indistinguishable from that of *E canis* by this rapid PCR assay, a positive result for *E ewingii/canis* indicates the presence of DNA from either of these 2 organisms.

**Reference Values:**
Negative

**Clinical References:**

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**Ehrlichia/Babesia Antibody Panel, Immunofluorescence, Serum**

**Clinical Information:** *Anaplasma phagocytophilum*: *Anaplasma phagocytophilum*, an intracellular rickettsia-like bacterium, preferentially infects granulocytes and forms inclusion bodies, referred to as morulae. A phagocytophilum is transmitted by *Ixodes* species ticks, which also transmit *Borrelia burgdorferi* and *Babesia* species. Infection with *A phagocytophilum* is also referred to as human granulocytic anaplasmosis (HGA) and symptoms in otherwise healthy individuals are often mild and nonspecific, including fever, myalgia, arthralgia, and nausea. Clues to the diagnosis of anaplasmosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated liver enzymes. HGA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. *Ehrlichia chaffeensis*: *Ehrlichia chaffeensis* is an intracellular rickettsia-like bacterium that preferentially infects monocytes and is sequestered in parasitophorous vacuoles referred to as morulae. Infections with *E chaffeensis* are also referred to as human monocytotropic ehrlichiosis (HME). *E chaffeensis* is transmitted by *Amblyomma* species ticks, which are found throughout the southeastern and south central United States. *Babesia microti*: Many cases of HME are subclinical or mild; however, the infection can be severe and life-threatening, particularly in immunosuppressed individuals. Reported mortality rates range from 2% to 3%. Fever, fatigue, malaise, headache, and other “flu-like” symptoms occur most commonly. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings. Babesiosis is a zoonotic infection caused by the protozoan parasite *Babesia microti*. The infection is acquired by contact with *Ixodes* ticks carrying the parasite. The deer mouse is the animal reservoir, and overall, the epidemiology of this infection is much like that of Lyme disease. Babesiosis is most prevalent in the Northeast, upper Midwest, and Pacific coast of the United States. Infectious forms (sporozoites) are injected during tick bites and the organism enters the vascular system where it infects red blood cells (RBC). In this intraerythrocytic stage it becomes disseminated throughout the reticuloendothelial system. Asexual reproduction occurs in RBC, and daughter cells (merozoites) are formed, which are liberated on rupture (hemolysis) of the RBC. Most cases of babesiosis are probably subclinical or mild, but the infection can be severe and life threatening, especially in older or asplenic patients. Fever, fatigue, malaise, headache, and other flu-like symptoms occur most commonly. In the most severe cases, hemolysis, acute respiratory distress syndrome, and shock may develop. Patients may have hepatomegaly and splenomegaly. A serologic test can be used as an adjunct in the diagnosis
and follow-up of babesiosis, when infection is chronic or persistent, or in seroepidemiologic surveys of
the prevalence of the infection in certain populations. Babesiosis is usually diagnosed by observing the
organisms in infected RBC on Giemsa-stained thin blood films of smeared peripheral blood. Serology
may also be useful if the parasitemia is too low to detect or if the infection has cleared naturally or
following treatment.

**Useful For:** As an adjunct in the diagnosis of infection with Anaplasma phagocytophilum, Ehrlichia
chaffeensis or Babesia microti Seroepidemiological surveys of the prevalence of the infection in certain
populations

**Interpretation:** Anaplasma phagocytophilum: A positive result of an immunofluorescence assay (IFA)
test (titer > or =1:64) suggests current or previous infection with human granulocytic ehrlichiosis. In
general, the higher the titer, the more likely it is that the patient has an active infection. Seroconversion
may also be demonstrated by a significant increase in IFA titers. During the acute phase of the infection,
serologic tests are often nonreactive, polymerase chain reaction (PCR) testing is available to aid in the
diagnosis of these cases (see EHRL / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood). Ehrlichia
chaffeensis: A positive immunofluorescence assay (titer > or =1:64) suggests current or previous
infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises
in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology
although antibody levels decline significantly during the year following infection. Babesia microti: A
positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous
infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an
active infection. Patients with documented infections have usually had titers ranging from 1:320 to
1:2,560.

**Reference Values:**

**ANAPLASMA PHAGOCYTOPHILUM**

<1:64

Reference values apply to all ages.

**EHRLICHIA CHAFFEENSIS**

<1:64

Reference values apply to all ages.

**BABESIA MICROTI**

<1:64

Reference values apply to all ages.

**Clinical References:** Centers for Disease Control and Prevention: Tickborne Diseases of the United
Services; 2017

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**Elastase, Pancreatic, Serum**

**Clinical Information:** Serum Elastase, also called Pancreatopeptidase, is a protease present in
pancreatic secretion with the unique ability to rapidly hydrolyze elastin. Elastin is a fibrillar protein found
in connective tissue. Elastin forms the elastic fibers found mostly in lungs and skin. Elastase is able to
hydrolyze denatured hemoglobin, casein, fibrin, albumin and denatured but not native collagen. Elastase
has been implicated in the pathogenesis of pulmonary emphysema, atherosclerosis and in the vascular
injury of acute pancreatic necrosis. Elastase activity is inhibited by protease inhibitors including
a1-Anti-Trypsin, a1-anti-Chymotrypsin, anti-Thrombin III, a2-Macroglobulin and b1-anti-Collagenase.
Patients with thyroid dysfunction have decreased Elastase activity. Serum pancreatic levels quantify EL 1
for the diagnosis or exclusion of an acute pancreatitis or an inflammatory episode of chronic pancreatitis
or gallstone induced pancreatitis.

**Reference Values:**

**Adult Reference Ranges:**

Normal pancreatic exocrine function:
Less than 3.5 ng/mL

No pediatric reference ranges available for this test.

**Elder, IgE, Serum**

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Electrolyte and Osmolality Panel, Feces**

**Clinical Information:** The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure.
Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin). Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars. There are multiple potential causes of osmotic diarrhea. Measurement of phosphate and/or magnesium in liquid stool can assist in identifying intentional or inadvertent use of magnesium and/or phosphate containing laxatives as the cause. The other causes of osmotic diarrhea include ingestion of osmotic agents such as sorbitol or polyethylene glycol laxatives, or carbohydrate malabsorption due to low stool pH (<6). Non-osmotic causes of diarrhea include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia. Secretory diarrhea is classified as non-osmotic and is caused by disruption of epithelial electrolyte transport when secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin are present. The fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (<50 mOsm/kg). Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms >4 weeks). Differentiating osmotic from non-osmotic causes of diarrhea is the goal of liquid stool testing. The primary way this is accomplished is through the measurement of sodium and chloride and calculation of the osmotic gap, which uses an assumed normal osmolality of 290 mOsm/kg rather than direct measurement of the osmolality. Measurement of osmolality can be useful in the evaluation of chronic diarrhea to help identify whether a specimen has been diluted with hypotonic fluid to simulate diarrhea. Chronic diarrhea with elevations in fecal chloride concentrations are caused by congenital chloridorrhea. This is a rare condition associated with a genetic defect in a protein responsible for transport of chloride ions across the mucosal membranes in the lower intestinal tract in exchange for bicarbonate ions. It plays an essential part in intestinal chloride absorption, therefore mutations in this gene have been associated with congenital chloride diarrhea. Acquired chloridorrhea is a rare condition which has been described as causing profuse, chloride-rich diarrhea and a surprising contraction metabolic alkalosis rather than metabolic acidosis often associated with typical diarrhea. Contributors to acquired chloridorrhea include chronic intestinal inflammation and reduction of chloride/bicarbonate transporter expression in genetically susceptible persons post-bowel resection and ostomy placement. Acquired chloridorrhea is rare but may be an under-recognized condition in post-bowel resection patients.

**Useful For:** Workup of cases of chronic diarrhea Diagnosis of factitious diarrhea (where patient adds water to stool to simulate diarrhea)

**Interpretation:** Osmotic Gap: Osmotic gap is calculated as 290 mOsm/kg-(2[Na]+2[K]). Typically, stool osmolality is similar to serum since the gastrointestinal (GI) tract does not secrete water. An osmotic gap above 50 mOsm/kg is suggestive of an osmotic component contributing to the symptoms of diarrhea. Magnesium-induced diarrhea should be considered if the osmotic gap is above 75 mOsm/kg and is likely if the magnesium concentration is above 110 mg/dL. An osmotic gap of 50 mOsm/kg or less is suggestive of secretory causes of diarrhea. A highly negative osmotic gap or a fecal sodium concentration greater than plasma or serum suggests the possibility of either sodium phosphate or sodium sulfate ingestion by the patient. Phosphorus: Phosphorus elevation above 102 mg/dL is suggestive of phosphate-induced diarrhea. Osmolality: Osmolality below 220 mOsm/kg indicates dilution with a hypotonic fluid. Sodium and Potassium: High sodium and potassium in the absence of an osmotic gap indicate active electrolyte transport in the GI tract that might be induced by agents such as cholera toxin or hypersecretion of vasointestinal peptide. Sodium: Sodium is typically found at lower concentrations (mean 30 +/- 5 mmol/L) in patients with osmotic diarrhea caused by magnesium-containing laxatives, while typically at higher concentrations (mean 104 +/- 5 mmol/L) in patients known to be taking secretory laxatives. Chloride: Chloride may be low (<20 mmol/L) in sodium sulfate-induced diarrhea. Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea.

**Reference Values:** An interpretive report will be provided

**Clinical References:** 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of

**ELPSR 113632**

**Electrolyte Panel, Serum**

**Clinical Information:** The electrolyte panel is ordered to identify electrolyte, fluid, or pH imbalance. Electrolyte concentrations are evaluated to assist in investigating conditions that cause electrolyte imbalances such as dehydration, kidney disease, lung diseases, or heart conditions. Repeat testing of the electrolyte or its components may be used to monitor the patient’s response to treatment of any condition that may be causing the electrolyte, fluid or pH imbalance. Electrolyte and acid-base imbalances can often be indicative of many acute and chronic illnesses. For this reason, the electrolyte panel is often used in the hospital and emergency settings to evaluate patients.

**Useful For:** Identifying a suspected imbalance in electrolytes or acid/base imbalance

**Interpretation:** With an imbalance of a single electrolyte, such as sodium or potassium, repeat testing may be ordered of that particular electrolyte, can be used to monitor the imbalance until remedied. With an acid-base imbalance, blood gases may be ordered, which will measure the oxygen, carbon dioxide, and pH levels in the arterial blood. These tests assist in evaluating the acuteness of the imbalance and monitoring the response to treatment.

**Reference Values:**

**SODIUM**

- <1 year: not established
- ≥1 year: 135-145 mmol/L

**POTASSIUM**

- <1 year: not established
- ≥1 year: 3.6-5.2 mmol/L

**CHLORIDE**

- <1 year: not established
- 1-17 years: 102-112 mmol/L
- ≥18 years: 98-107 mmol/L

**BICARBONATE**

**Males**

- <1 year: not established
- 1-2 years: 17-25 mmol/L
- 3 years: 18-26 mmol/L
- 4-5 years: 19-27 mmol/L
- 6-7 years: 20-28 mmol/L
- 8-17 years: 21-29 mmol/L
- ≥18 years: 22-29 mmol/L

**Females**
<1 year: not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: not established
> or =7 years: 7-15


Electron Microscopy, Varies

Clinical Information: Transmission electron microscopy (TEM) is an important diagnostic tool used in the comprehensive assessment of human disease and is most often used in conjunction with other methods such as light microscopy and immunohistopathological techniques. This fundamental technology can provide both confirmatory and diagnostic value to the pathologist and clinician.

Useful For: Providing information to aid in the diagnosis of medical disorders such as storage diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and primary ciliary dyskinesia

Interpretation: The images and case histories are correlated and interpreted by a pathologist who is an expert in the field of the suspected diagnoses. Results will be provided by telephone. If requested, representative images showing diagnostic features will be sent.

Reference Values: An interpretive report will be provided.


Electrophoresis, Protein, 24 Hour, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis:
- Albumin
- Alpha-1
- Alpha-2
- Beta-globulin
- Gamma-globulin
The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available in Special Instructions:
- Laboratory Approach to the Diagnosis of Amyloidosis
- Laboratory Screening Tests for Suspected Multiple Myeloma

Useful For: Monitoring patients with monoclonal gammopathies

Interpretation: A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration should be followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin heavy chain fragments as well as free light chains may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) that is predominantly
albumin is consistent with amyloidosis (AL) or light chain deposition disease (LCDD). Because patients with AL and LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

**Reference Values:**

- **PROTEIN, TOTAL**
  
  $<229 \text{ mg/24 hours}$

Reference values have not been established for patients $<18$ years of age. Reference value applies to 24-hour collection.

**ELECTROPHORESIS, PROTEIN**

The following fractions, if present, will be reported as mg/24 hours:

- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin
- Gamma-globulin

**Clinical References:**


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**Electrophoresis, Protein, Random, Urine**

**Clinical Information:** Urine proteins can be grouped into 5 fractions by protein electrophoresis:

- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin
- Gamma-globulin

The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The following algorithms are available in Special Instructions: - Laboratory Approach to the Diagnosis of Amyloidosis - Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Identifying monoclonal gammopathies using random urine specimens

**Interpretation:** A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration should be followed by immunofixation to identify the immunoglobulin heavy chains and light chains. Immunoglobulin heavy chain fragments as well as free light chains may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of greater than $1 \text{ g/24 hours}$ is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein $>3 \text{ g/24 hours}$) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) and light-chain deposition disease (LCDD). Because patients with AL and LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

**Reference Values:**

- **PROTEIN, TOTAL**
  
  No reference values apply to random urine.

- **ELECTROPHORESIS, PROTEIN**
  
  The following fractions, if present, will be reported as mg/dL:
  
  - Albumin
  - Alpha-1-globulin
-Alpha-2-globulin
-Beta-globulin
-Gamma-globulin

No reference values apply to random urines.


**SPEP** 97408

**Electrophoresis, Protein, Serum**

**Clinical Information:** This profile includes both total protein and protein electrophoresis. The serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and C3 -Gamma, composed primarily of immunoglobulins The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

**Useful For:** Screening patients with suspected monoclonal gammopathies Diagnosis of monoclonal gammopathies, when used in conjunction with matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) and free light chain analysis

**Interpretation:** Monoclonal Gammopathies: A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma-globulin region and, more rarely, in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein and should be confirmed by immunoaffinity-purification matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) to identify any immunoglobulin heavy or light chains. A MPSU / Monoclonal Protein Study, 24 Hour, Urine is suggested for first-time M-spike patients to assess for renal disease that can be associated with an M-spike. -A monoclonal IgG or IgA greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and should not be used to screen for the disorder. The DMOGA / Monoclonal Gammopathy, Diagnostic, Serum, which includes MALDI-TOF MS, and serum free light chains, conforms to the International Myeloma Working Group (IMWG) guidelines for screening and should be performed if there is clinical suspicion. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1
g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1- Antitrypsin, Serum).

Reference Values:
TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.
Reference values have not been established for patients that are <16 years of age.


Electrophoresis, Protein, Serum
Clinical Information: Serum proteins can be grouped into 5 fractions by protein electrophoresis:
-Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and C3 -Gamma, composed primarily of immunoglobulins The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

Useful For: Monitoring patients with monoclonal gammopathies Diagnosis of monoclonal gammopathies

Interpretation: Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma-globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin heavy chain and/or light chain. -A monoclonal IgG or IgA greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. -After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region
(most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and should not be used to screen for the disorder. The MPSS / Monoclonal Protein Study, Serum, which includes immunofixation, and FLCP / Immunoglobulin Free Light Chains, Serum should be done to screen if the clinical suspicion is high.

Other Abnormal PEL Findings:
- A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease.
- A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome.
- A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypalbuminemia), the affected fraction is faint or absent. An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1- Antitrypsin, Serum).

**Reference Values:**

**PROTEIN, TOTAL**

| > or =1 year | 6.3-7.9 g/dL |

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

**PROTEIN ELECTROPHORESIS**

- Albumin: 3.4-4.7 g/dL
- Alpha-1-globulin: 0.1-0.3 g/dL
- Alpha-2-globulin: 0.6-1.0 g/dL
- Beta-globulin: 0.7-1.2 g/dL
- Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report.

Reference values have not been established for patients that are less than 16 years of age.

**Clinical References:**


**Clinical Information:**

Elm, IgE, Serum

Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to elm. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode. - To confirm sensitization prior to beginning immunotherapy. - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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

Reference Values:

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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>2</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


EMR 113366

EM, Renal Biopsy (Bill Only)

Reference Values:

This test is for billing purposes only.
This is not an orderable test.

EMICZ 610074

Emicizumab, Modified One Stage Assay Factor VIII, Plasma

Clinical Information: Emicizumab (Hemlibra) is a bi-specific antibody directed toward factor IXa and factor X, bridging in close enough proximity to mimic and replace factor VIII. Emicizumab has been approved by the Food and Drug Administration for prevention of bleeding in hemophilia A patients, both with and without inhibitors to factor VIII. In clinical trials, clinical outcomes were achieved without the measurement of plasma emicizumab levels to inform and make management decisions. However, in selected clinical situations, measurement of drug level would be useful. (eg. For patients experiencing break through bleeding episodes, if levels are not detectable or below the published [observed] ranges, this may imply noncompliance or development of an antidrug antibody.)

Useful For: Monitoring compliance or potential development of an antidrug antibody. This assay is not indicated for monitoring factor VIII infusions or for making a diagnosis of hemophilia.

Interpretation: Therapeutic ranges for plasma emicizumab concentrations have not been established. Trough plasma concentrations observed during clinical trials ranged between 35 and 55 micrograms/mL.

Reference Values:

<1 mcg/mL.
**Encainide (Enkaidr), ODE and MODE**

**Reference Values:**

- **Encainide:**
  - Reference Range: 15 - 100 ng/mL

- **O-Demethylenencainide (ODE):**
  - Reference Range: 100 - 300 ng/mL

- **3-Methoxy-ODE (MODE):**
  - Reference Range: 60 - 300 ng/mL

10% of patients do not form therapeutic concentrations of the active metabolites, ODE and MODE. In these patients the recommended range for the encainide concentration is 300 - 1200 ng/mL.

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**Encephalopathy, Autoimmune Evaluation, Serum**

**Clinical Information:** Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of one or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, leucine-rich glioma inactivated protein: LGI1 and contactin associated protein 2: CASPR2), ionotropic glutamate receptors (N-methyl-D-aspartate receptor: NMDA and 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid: AMPA), metabotropic gamma-aminobutyric acid (GABA)-B receptors; 2) enzymes, signaling molecules and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (glutamic acid decarboxylase 65: GAD65, collapsin response-mediator protein-5 neuronal: CRMP-5, antineuronal nuclear antibody-type 1: ANNA-1, and ANNA-2). Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identify patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms, onset rapidly progressive course, and fluctuating symptoms) and radiological findings consistent with...
inflammation, 2) detection of neural autoantibodies in serum or cerebrospinal fluid (CSF), and 3) favorable response to a trial of immunotherapy. Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, LGI1 antibody was initially considered to be specific for autoimmune limbic encephalitis, but over time other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia.

Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (ANNA-1, CRMP-5-IgG), ovarian teratoma (NMDA-R), and thymoma (CRMP-5 IgG). An individual patient's profile autoantibody may be informative for a specific cancer type. For example, in a patient presenting with encephalitis who has CRMP 5 IgG, and subsequent reflex reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and GFAP-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing.

**Useful For:** Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation in serum specimens The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Inflammatory cerebral spinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

**Interpretation:** Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy: -Plasma membrane autoantibodies: N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor; neuronal ACh receptor. These are all potential effectors of neurological dysfunction. -Neuronal nuclear autoantibodies, type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3) -Neuronal or muscle cytoplasmic antibodies: amphiphysin, Purkinje cell antibodies (PCA-1) and PCA-2, CRMP-5, GAD65, or striational

**Reference Values:**

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**Encephalopathy, Autoimmune Evaluation, Spinal Fluid**

Clinical Information: Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappopriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of one or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, leucine-rich glioma inactivated protein: LGII and contactin associated protein 2: CASPR2), ionotropic glutamate receptors (N-methyl-D-aspartate receptor: NMDA and...
2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl]propanoic acid: AMPA), metabotropic gamma-aminobutyric acid (GABA)-B receptors; 2) enzymes, signaling molecules and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (glutamic acid decarboxylase 65: GAD65, collapsin response-mediator protein-5 neuronal: CRMP-5, antineuronal nuclear antibody-type 1: ANNA-1, and ANNA-2). Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identify patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms, onset rapidly progressive course, and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebrospinal fluid (CSF), and 3) favorable response to a trial of immunotherapy. Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, LGI1 antibody was initially considered to be specific for autoimmune limbic encephalitis, but over time other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (ANNA-1; CRMP-5-IgG), ovarian teratoma (NMDA-R), and thymoma (CRMP-5-IgG). An individual patient's profile of autoantibody may be informative for a specific cancer type. For example, in a patient presenting with encephalitis who has CRMP-5-IgG, and subsequent reflex reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and GFAP-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing.

**Useful For:** Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dysdyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation in spinal fluid specimens. The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Inflammatory cerebrospinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

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**Reference Values:**

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<td>AMPCC</td>
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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 926
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<td>PCA2C</td>
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Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, ANNA-3, CRMP-5-IgG, PCA-1, PCA-2, or PCA-Tr may be reported as “unclassified anti-neuronal IgG.” Complex patterns that include nonneuronal elements may be reported as “uninterpretable.” Note: CRMP-5 titers lower than 1:2 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored spinal fluid (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 to request CRMP-5 Western blot.


Endometrial Stromal Tumors (EST), 7p15 (JAZF1), 6p21.32 (PHF1), 17p13.3 (YWHAE) Rearrangement, FISH, Tissue

Clinical Information: Endometrial stromal tumors (EST) arise from the uterus and include the benign endometrial stromal nodule (ESN) and infiltrative endometrial stromal sarcoma (ESS). These tumors are characterized by a translocation that fuses JAZF1 at 7p15 to IJAZ1 at 17q21 or a variant 6;7 translocation involving JAZF1 and PHF1. Published literature employing FISH and reverse transcriptase PCR (RT-PCR) suggests rearrangement of JAZF1 occurs in approximately 76% of ESN and approximately 58% of ESS. JAZF1 is not generally considered to be involved in the genetic mechanism of the high-grade undifferentiated endometrial sarcoma (UES), although rarely some cases of UES are positive for JAZF1, which may reflect the presence of an ESS component. For PHF1 disruption, a study
of 94 EST demonstrated the following: -PHF1/JAZF1 fusion in 4 primary ESS -PHF1/EPC1 fusion in 2 primary ESS and 1 extrauterine ESS -PHF1 rearrangement without a known partner in 6 primary or metastatic ESS and 1 extrauterine ESS JAZF1/JJAZ1, PHF1/JAZF1 and PHF1/EPC1 fusions were mutually exclusive in individual patients. No rearrangement of PHF1 was found in ESN, UES, or non-EST tumors in the differential diagnosis. These results indicate that PHF1 can rearrange with both known and unknown partners in addition to JAZF1 and is potentially specific for ESS. In high-grade ESS, a recurrent t(10;17)(q22;p13) resulting in fusion of YWHAE (also called 14-3-3epsilon at 17p13.3 with either FAM22A or FAM22B was identified. In contrast, JAZF1 rearrangements are typically observed in low-grade ESS. JAZF1 and YWHAE rearrangements are mutually exclusive and have distinct gene expression profiles. YWHAE rearrangement is potentially specific for high-grade ESS as no YWHAE disruption has been reported in other uterine or nonuterine mesenchymal tumors. The clinical utility of identifying JAZF1 rearrangement is mainly to address the differential diagnostic dilemma that occurs when ESS are present as metastatic lesions or exhibit variant morphology. In JAZF1-negative EST cases, reflex genetic analysis to identify PHF1 or YWHAE rearrangement increases the diagnostic sensitivity for EST. In addition, confirmation of YWHAE rearrangement may have prognostic implications as YWHAE defines a distinct, clinically more aggressive and histologically higher grade subgroup of ESS compared to those with JAZF1 rearrangements.

**Useful For:** Supporting the diagnosis of endometrial stromal tumors when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an endometrial stromal tumor of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Endomysial Antibodies, IgA, Serum**

**Clinical Information:** Circulating IgA endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. Because of the high specificity of endomysial antibodies for celiac disease, this test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

**Useful For:** Analysis of IgA-endomysial antibodies for the diagnosis of dermatitis herpetiformis and celiac disease.
celiac disease Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

**Interpretation:** The finding of IgA-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgA-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgA-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining or other factors; in this case, the results will be recorded as "indeterminate." In this setting, further testing with measurement of TTGA / Tissue Transglutaminase Antibody, IgA, Serum and IGA / Immunoglobulin A (IgA), Serum levels are recommended.

**Reference Values:**
Negative in normal individuals; also negative in dermatitis herpetiformis or celiac disease patients adhering to gluten-free diet.

**Clinical References:**

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**Endomysial Antibodies, IgA, Titer, Serum**

**Clinical Information:** Circulating IgA endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. Because of the high specificity of endomysial antibodies for celiac disease, the test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

**Useful For:** Confirmation of a positive IgA-endomysial antibodies result

**Interpretation:** The finding of IgA-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgA-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgA-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining or other factors; in this case, the results will be recorded as "indeterminate." In this setting, further testing with measurement of TTGA / Tissue Transglutaminase Antibody, IgA, Serum and IGA / Immunoglobulin A (IgA), Serum levels are recommended.

**Reference Values:**
Only orderable as a reflex. For more information see EMA / Endomysial Antibodies, IgA, Serum.

**Clinical References:**
Endomysial Antibodies, IgG, Serum

Clinical Information: Circulating IgG endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. Because of the high specificity of endomysial antibodies for celiac disease, the test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

Useful For: Analysis of IgG-endomysial antibodies for the diagnosis of dermatitis herpetiformis and celiac disease Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: The finding of IgG-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgG-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgG-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining or other factors; in this case, the results will be recorded as "indeterminate." In this setting, further testing with measurement of TTGA / Tissue Transglutaminase Antibody, IgA, Serum and IGG / Immunoglobulin G (IgG), Serum levels are recommended.

Reference Values:
Negative in normal individuals; also negative in patients with either dermatitis herpetiformis or celiac disease while adhering to gluten-free diet.


English Plantain, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to English plantain Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>Positive</td>
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</tr>
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<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Entamoeba histolytica Antibody, Serum**

**Clinical Information:** Amebiasis is an infection by the protozoan parasite, Entamoeba histolytica. The infection is acquired by ingestion of cysts in fecally contaminated food or water; excystation and infection occur in the large intestine. After excystation, trophozoites attach to the intestinal wall and liberate extracellular enzymes that enable invasion of the mucosa and spread to other organs, especially the liver and lung where abscesses develop. Amebiasis (or amebic dysentery) can cause bloody diarrhea accompanied by fever and prostration. White and red blood cells are found in the stool. Liver abscess can develop several weeks to months later producing hepatomegaly and fever. Pathogenic (E histolytica) and nonpathogenic (Entamoeba dispar) species of Entamoeba occur. Additionally, some of those infected with pathogenic strains are asymptomatic cyst carriers. Serology may be particularly useful in supporting the diagnosis of amebic liver abscess in patients without a definite history of intestinal amebiasis and who have not spent substantial periods of time in endemic areas.

**Useful For:** As an adjunct in the diagnosis of extraintestinal amebiasis, especially liver abscess

**Interpretation:** A positive result suggests current or previous infection with Entamoeba histolytica. Since pathogenic and nonpathogenic species of Entamoeba cannot be differentiated microscopically, some authorities believe a positive serology indicates the presence of the pathogenic species (ie, E histolytica).

**Reference Values:** Negative

Reference values apply to all ages.


**Entamoeba histolytica Antigen, EIA**

**Clinical Information:** Amebiasis is an infection by the protozoan parasite, Entamoeba histolytica. The infection is acquired by ingestion of cysts in fecally contaminated food or water; excystation and infection occur in the large intestine. After excystation, trophozoites attach to the intestinal wall and liberate extracellular enzymes that enable invasion of the mucosa and spread to other organs, especially the liver and lung where abscesses develop. Amebiasis (or amebic dysentery) can cause bloody diarrhea accompanied by fever and prostration. White and red blood cells are found in the stool. Liver abscess can develop several weeks to months later producing hepatomegaly and fever. Pathogenic (E histolytica) and nonpathogenic (Entamoeba dispar) species of Entamoeba occur. Additionally, some of those infected with pathogenic strains are asymptomatic cyst carriers. Serology may be particularly useful in supporting the diagnosis of amebic liver abscess in patients without a definite history of intestinal amebiasis and who have not spent substantial periods of time in endemic areas.

**Useful For:** As an adjunct in the diagnosis of extraintestinal amebiasis, especially liver abscess

**Interpretation:** A positive result suggests current or previous infection with Entamoeba histolytica. Since pathogenic and nonpathogenic species of Entamoeba cannot be differentiated microscopically, some authorities believe a positive serology indicates the presence of the pathogenic species (ie, E histolytica).

**Reference Values:** Negative

Reference values apply to all ages.

Clinical Information: Entamoeba histolytica are intestinal parasites that infect a half billion people worldwide annually. Of those infected, most are infected with the non-pathogenic E. dispar, which has not been associated with disease. It is estimated that approximately 10% of the half billion people infected each year are infected with the pathogenic E. histolytica. These individuals become symptomatic and develop colitis and liver abscesses. Limitations: Extraintestinal amebiasis is frequently found without trophozoites or cysts in stool: patients may have a negative stool antigen result.

Reference Values:
Entamoeba histolytica Antigen: Not Detected

Enteric Pathogens Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals) and these agents may result in similar symptoms. A thorough patient history covering symptoms, severity, duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician categorize the disease and ensure that any special requests are communicated to the laboratory.

Useful For: Determining whether a bacterial enteric pathogen is the cause of diarrhea May be helpful in identifying the source of the infectious agent (eg, dairy products, poultry, water, or meat) This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of an enteric pathogen identifies the cause of diarrhea.

Reference Values:
No growth of pathogens


Enterovirus, Molecular Detection, PCR, Plasma

Clinical Information: Enteroviruses are positive-sense RNA viruses in the Picornaviridae family. These viruses were initially classified by serotype as polioviruses (3 types), echoviruses (31 types, including types 22 and 23, which are now classified as parechoviruses), coxsackievirus A (23 types), and coxsackievirus B (6 types). However, genomic studies have demonstrated that there is significant overlap in the biological characteristics of different serotypes and, more recently, isolated enteroviruses are now named with consecutive numbers (eg, EV68, EV69). The normal site of enterovirus replication is the gastrointestinal tract where the infection is typically subclinical. However, in a proportion of cases, the virus spreads to other organs, causing systemic manifestations, including mild respiratory disease (eg, common cold); conjunctivitis; hand, foot, and mouth disease; aseptic meningitis; myocarditis; and acute flaccid paralysis. Collectively, enteroviruses are the most common cause of upper respiratory tract disease in children. In addition, the enteroviruses are the most common cause of central nervous system (CNS) disease; they account for almost all viruses recovered in culture from spinal fluid. Differentiation of enteroviruses from other viruses and bacteria that cause CNS disease is important for the appropriate medical management of these patients. Traditional cell culture methods require 6 days, on average, for enterovirus detection. In comparison, real-time PCR allows same-day detection. Detection of enterovirus nucleic acid by PCR is also the most sensitive diagnostic method for
the diagnosis of CNS infection caused by these viruses.

Useful For: Aids in diagnosing enterovirus infections

Interpretation: A positive result indicates the presence of enterovirus RNA in the specimen.

Reference Values:

Negative

**EOSU1**

**Eosinophils, Random, Urine**

**Clinical Information:** Eosinophils are white blood cells that normally do not appear in urine. The presence of eosinophils in the urine is seen in acute interstitial nephritis, which is caused by an allergic reaction, typically to drugs.

**Useful For:** Investigation of possible acute interstitial nephritis

**Interpretation:** Results of greater than 5% eosinophils are indicative of acute interstitial nephritis; results between 1% and 5% eosinophils are indeterminant.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Clinical References:**

**FEPHD**

**Ephedrine, Serum**

**Reference Values:**

Reference Range: 35 - 80 ng/mL

**EPUR**

**Epicoccum purpurascens, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Epicoccum purpurascens Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<tr>
<td>0</td>
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<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Epidermal Nerve Fiber Density Consultation, Varies

Clinical Information: Small fiber peripheral neuropathy is a common neurological complaint and a frequent source of morbidity in many patient populations. Direct investigation of small fiber involvement has been limited to most classical techniques such as electromyography (EMG), nerve conduction studies (NCS), and nerve biopsy, focus on large diameter nerve fibers and may be normal in patients with small fiber neuropathies. The advent of epidermal skin biopsies and PGP 9.5 immunohistochemistry allows the direct visualization and morphologic assessment of small sensory fibers innervating the skin. (1) Assessment of intraepidermal nerve fiber density has been used to reliably demonstrate pathologic abnormalities in small fiber neuropathy of various etiologies including diabetes, HIV, systemic lupus erythematosus, and neurosarcoïdosis. Further, the technique has been validated, shown to have acceptable sensitivity and specificity, and is minimally invasive. The publication of normative data for commonly tested sites such as the distal and proximal legs and arms permits direct comparison of patients to age- and sex-matched controls facilitating localization and diagnosis. (2-4) Based on class 1 evidence and American Medical Association CPT code review process acceptance, intraepidermal nerve fiber density (IENFD) measurements are now an accepted investigational method in the workup of polyneuropathy, including the characterization and diagnosis of varieties of length-dependent small fiber polyneuropathies. IEFND measurements have been incorporated in recent practice guidelines published by the American Academy of Neurology and the European Federation of Neurological Science. (5,6)

Useful For: Investigation of polyneuropathies

Interpretation: The number of intraepidemically originating nerve fibers that cross the basement membrane between the dermis and epidermis are counted in several sections. (2,5) The total linear length of the epidermis is measured using standard morphometric techniques and a density of epidermal nerve fibers (number of fibers/mm) is reported. This value is compared to previously published normative data.

Reference Values:
A consultative report will be provided.

Epidermophyton floccosum IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Epilepsy, Autoimmune Evaluation, Serum

**Clinical Information:** Antiepileptic drugs (AED) are the mainstay of treatment for epilepsy but seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders, including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis. Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. The advent of more sensitive and specific serological detection methods is increasingly revealing previously underappreciated autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis. Autoantibody specificities currently most informative for autoimmune epilepsies include leucine-rich glioma inactivated protein-1 (LGI1), glutamic acid decarboxylase-65 (GAD65), N-methyl-D-aspartate receptor (NMDA-R), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-R), and gamma aminobutyric acid type B receptor (GABA-B-R) antibodies. Autoantibodies recognizing onconeural proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody, type 1: ANNA 1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG; N-type calcium channel antibody), also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient’s autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of cerebrospinal fluid (CSF) and serum for neural autoantibodies. Selective testing for individual autoantibodies is not advised because each is individually rare, and a timely diagnosis is critical. Collectively, the antibodies tested for in the autoimmune epilepsy evaluations represent a broad spectrum of treatable disorders, some of which are associated with occult cancer. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and GFAP-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

**Useful For:** Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of less than 2 years using serum specimens Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency), or multiple sclerosis -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without obvious cause, especially in a patient with past or family history of cancer -A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological
markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia. - Plasma membrane antibodies (N-methyl-D-aspartate: NMDA receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid: AMPA receptor; gamma-amino butyric acid: GABA-B receptor). These autoantibodies are all potential effectors of dysfunction. - Antineuronal nuclear antibody, type 1 (ANNA-1) or type 3 (ANNA-3). - Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2: PCA-2, collapsin response-mediator protein-5 neuronal: CRMP-5-IgG, or glutamic acid decarboxylase: GAD65 antibody).

Reference Values:

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Test ID | Reporting Name                        | Methodology | Reference Value |
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**Clinical References:**
Clinical Information: Antiepileptic drugs (AEDs) are the mainstay of treatment for epilepsy, but seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders, including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis. Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. The advent of more sensitive and specific serological detection methods is increasingly revealing previously underappreciated autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis. Autoantibody specificities currently most informative for autoimmune epilepsies include leucine-rich glioma inactivated protein-1 (LGII), glutamic acid decarboxylase-65 (GAD65), N-methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), and gamma aminobutyric acid type B receptor (GABABR) antibodies. Autoantibodies recognizing onconeural proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody, type 1: ANNA 1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG; N-type calcium channel antibody), also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient’s autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of cerebrospinal fluid (CSF) and serum for neural autoantibodies. Selective testing for individual autoantibodies is not advised because each is individually rare, and a timely diagnosis is critical. Collectively, the antibodies tested for in the autoimmune epilepsy evaluations represent a broad spectrum of treatable disorders, some of which are associated with occult cancer. Testing of CSF for autoimmune epilepsies is particularly helpful when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and GFAP-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGII antibody is more sensitive than CSF testing. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

Useful For: Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of less than 2 years using spinal fluid specimens Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency) or "multiple sclerosis" -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without obvious cause, especially in a patient with past or family history of cancer

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient’s immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune epilepsy: -Plasma membrane antibodies (N-methyl-D-aspartate: NMDA receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid: AMPA receptor; gamma-aminobutyric acid: GABA-B receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 1: ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2: PCA-2, collapsin response-mediator protein-5 neuronal: CRMP-5-IgG, or glutamic acid decarboxylase: GAD65 antibody). A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence.

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PC1BC  PCA-1 Immunoblot, CSF  IB  Negative
PCTBC  PCA-Tr Immunoblot, CSF  IB  Negative
PCA1C  Purkinje Cell Cytoplasmic Ab Type 1  IFA  Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, ANN3C, CA-1, PCA-2, or PCA-Tr may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable." Note: CRMP-5 titers lower than 1:2 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored spinal fluid (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 to request CRMP-5 Western blot.


Clinical Information: Epilepsy is a heterogeneous group of disorders that are characterized by recurrent and usually unprovoked seizures. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for the heterogeneous epilepsy and seizure disorders and, therefore, establish long-term prognosis. Early Epileptic Encephalopathy Panel: Epileptic encephalopathies are neurodevelopmental disorders caused by recurrent clinical seizures usually seen during the early infantile period. Early epileptic encephalopathy is associated with impaired cognitive, sensory, and motor development. The most common causes of early epileptic encephalopathy include structural brain defects and inborn errors of metabolism, but genetic factors have been found to have an increasing role in cases without structural or metabolic causes. Infantile Spasms Panel: Infancy is the highest risk period for epileptic seizures, and infantile spasms are the most frequent type of epilepsy in the first year of life. Infantile spasms are characterized by spasms that occur in clusters and usually have an onset before 2 years of age. A spasm involves a brief contraction followed by less intense, but sustained, tonic contraction lasting up to 1 to 2 seconds. Additionally, infantile spasms are associated with a distinguishing electroencephalogram (EEG) pattern called hyposrrhythmia that has random, high-voltage spikes and slow waves. However, hyposrrhythmia is not seen in all cases of infantile spasms. Infantile spasms seen in addition to hyposrrhythmia and delayed brain development or regression are referred to as
West syndrome. Other subgroups of infantile spasms include infantile spasms single-spasm variant (ISSV), in which spasms occur singly rather than in clusters; hypersarrhythmia without infantile spasms (HWIS), when hypersarrhythmia occurs without any evidence of spasms; and infantile spasms without hypersarrhythmia (ISW), when clinical spasms occur without hypersarrhythmia. Febrile Seizure Panel: Febrile seizures are the most common convulsive event in childhood, usually occurring between 3 months and 5 years of age, and can be the presenting symptom of many clinical epilepsy syndromes. They are associated with fever, but without evidence of intracranial infection or defined cause. The most significant risk factors for recurrence of febrile seizures are family history of febrile seizures, a relatively low grade of fever, a shorter duration of fever before seizure, and onset of first seizure before 18 months of age. Most children with febrile seizures do not develop epilepsy. However, the risk to develop unprovoked seizures after a febrile seizure is 2 to 3 times the risk of epilepsy in the general population. The most significant risk factors for the development of epilepsy include developmental delay or an abnormal neurological examination before the onset of the febrile seizure, a history of complex febrile seizures, and a first-degree relative with epilepsy. The most common epilepsy syndromes that present with febrile seizures include genetic epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome. GEFS+ is an epilepsy syndrome in which febrile seizures continue beyond 6 years of age. Dravet syndrome is a neurodevelopment disorder associated with severe myoclonic epilepsy of infancy and often begins with prolonged seizures triggered by fever. Progressive Myoclonic Epilepsy Panel: Progressive myoclonic epilepsies are a genetically heterogeneous group of disorders that are characterized by worsening action myoclonus, epileptic seizures, and a progressive neurologic decline. The most common forms of progressive myoclonic epilepsies include Unverricht-Lundborg disease, Lafora disease, neuronal ceroid lipofuscinoses, and sialidoses. The first symptom of Unverricht-Lundborg disease is typically involuntary myoclonic jerks and it presents around 6 to 15 years of age. Lafora disease presents around 12 to 17 years of age, with many individuals having isolated febrile or nonfebrile convulsions in infancy or early childhood. Individuals with a neuronal ceroid lipofuscinosis have progressive decline, an evolving cognitive and motor disorder, and seizures. Neuronal Migration Disorders Panel: Neuronal migration disorders are caused by abnormal migration of neurons in the developing brain and nervous system. Neuronal migration disorders include lissencephaly, heterotopia, polymicrogyria, schizencephaly, and focal cortical dysgenesis. Lissencephaly, which means smooth brain, is characterized by the lack of normal cortical folds or gyria. Severity of the disorder ranges from absence (agyria) to reduction (pachygyria) of normal gyral patterns. Classical lissencephaly, also known as type 1 lissencephaly, consists of early developmental delay, mental retardation, and spastic quadriplegia. Seizures are present in almost all children with early onset, in addition to a high prevalence of infantile spasms. In addition, seizures typically develop with classical lissencephaly in the first 6 to 12 months of life. Neuronal heterotopia is characterized by a cluster of disorganized neurons in abnormal locations and is divided into periventricular nodule heterotopia and subcortical band heterotopia. Periventricular nodular heterotopia has a wide spectrum of clinical features, which can include developmental delay, microcephaly, and infantile spasms. However, epilepsy is the main feature. Subcortical band heterotopia has a spectrum of cognitive function ranging from normal to severe cognitive impairment, and features intractable epilepsy. Polymicrogyria is characterized by an irregular brain surface with an excessive number of small and partly fused gyria separated by shallow sulci. Children can present with developmental delay and mild spastic quadriplegia, and almost all affected children have a high risk of developing epilepsy.

Schizencephaly is a disorder of cortical organization and can be divided into closed or fused lips, also known as type I, or open lips, also known as type II. Individuals with unilateral closed-lip schizencephaly generally have mild hemiparesis and seizures, but no impairment of normal developmental milestones. Individuals with open-lip schizencephaly have mild-to-moderate developmental delay and hemiparesis. Individuals with bilateral clefts typically have more severe cognitive impairment and severe motor abnormalities. Focal cortical dysgenesis is a congenital abnormality of cortical development that is generally associated with intractable focal epilepsy starting in adolescence. However, seizures associated with focal cortical dysgenesis may arise at any age. Focal Epilepsy Panel: Focal epilepsy is a neurological disorder characterized by recurrent seizures with abnormal electrographic activity in localized brain areas. Focal epilepsy can develop at any point during life. However, genetic causes of focal epilepsy are often associated with an earlier onset. They are comprised of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial mesial temporal lobe epilepsy, autosomal dominant lateral temporal lobe epilepsy (ADLTE), and autosomal dominant partial epilepsy with variable loci. ADNFLE is characterized by frontal lobe seizures occurring during sleep, often in clusters. The seizures are short in duration, fundamentally motor-based, and transmitted in an autosomal dominant pattern. Familial mesial temporal lobe epilepsy has an adolescent or adult onset that consists of seizures with symptoms that are psychic,
autonomic, or sensorial. ADLTE is characterized by partial visual or auditory seizures that manifest in the first 2 decades of life and is transmitted in an autosomal dominant pattern. Autosomal dominant partial epilepsy with variable loci is characterized by focal seizures arising from different brain regions in different members of the same family. Most individuals have seizures of frontal or temporal origin and the age of onset is variable. Epilepsy with Migraine Panel: Epilepsy, which is multiple unprovoked seizures, is diverse with heterogeneous genetic causes. Additionally, it is one of the most common neurological diseases globally. People with epilepsy are more likely to be diagnosed with migraine than are people in the general population. Epilepsy and migraines share clinical features, and migraines are one of the most common neurologic comorbidities in individuals with epilepsy. The association between migraine and epilepsy is bilateral with either proceeding or following the other, or they may occur at the same time. Encephalopathy with Seizures Panel: Epileptogenic encephalopathies are neurodevelopmental disorders caused by recurrent clinical seizures usually seen during the early infantile period. However, this panel is targeted towards those cases of encephalopathy with an onset outside of the neonatal and infantile periods.

Tuberous Sclerosis Panel: Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous multisystem disorder associated with mutations in the TSC1 and TSC2 genes. TSC involves abnormalities of the skin, brain, kidneys, heart, and lungs. Central nervous system tumors are the leading cause of morbidity and mortality. Brain abnormalities can include infantile spasm and hypsarrhythmia syndrome. Custom Gene Panel: Custom gene ordering allows the creation of a custom gene list to tailor testing to a patient's exact need. After selection of a specific disease state, the custom gene panel can be modified to add or remove genes. Through this option single gene testing can be performed.

Useful For: Establishing a diagnosis of an epilepsy or seizure disorder associated with known causal genes Identifying mutations within genes known to be associated with inherited epilepsy or seizure disorders, allowing for predictive testing of at-risk family members

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

Reference Values: An interpretive report will be provided.


Epithelia Panel # 1, Serum

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>3 3.50-17.4</td>
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</tr>
<tr>
<td>4 17.5-49.9</td>
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</tr>
<tr>
<td>5 50.0-99.9</td>
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| 6 > 100       | Strongly positive Reference values apply to all ages.


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**Epithelia Panel # 2, Serum**

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


**EMAI 70424**

**Epithelial Membrane Antigen (EMA) Immunostain, Technical Component Only**

**Clinical Information:** Epithelial membrane antigen (EMA), also known as mucin 1 (MUC1), is expressed by epithelial cells of all types, mesothelial cells, perineural cells, and a subset of plasma cells. EMA is expressed by meningiomas, synovial sarcoma, epithelioid sarcoma, a subset of peripheral nerve sheath tumors, the lymphocyte-predominant cells of lymphocyte-predominant Hodgkin lymphoma, and anaplastic large cell lymphoma. Diagnostically, EMA is useful in recognizing epithelial derivation of poorly differentiated malignant tumors and, in conjunction with a panel of mucin markers (MUC2, MUC5AC, and MUC6), may be used in subtyping intraductal papillary mucinous neoplasms.

**Useful For:** Recognizing epithelial derivation of poorly differentiated malignant tumors Subtyping intraductal papillary mucinous neoplasms when used in conjunction with mucin (MUC) 2, MUC5AC and MUC6

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

EBNA2

Epstein Barr Nuclear Antigen 2 (EBNA2) Immunostain, Technical Component Only

Clinical Information: Epstein Barr virus (EBV) nuclear antigen 2 (EBNA2) is an EBV-encoded nuclear protein of 82 kD. EBNA2 is necessary for transformation of EBV-infected B lymphocytes and has been shown to modulate the activity of several viral and cellular promoters. This immunostain may be useful in the diagnosis of reactive and neoplastic lymphoproliferative and plasma cell proliferative disorders.

Useful For: Identification of Epstein Barr virus infection in normal, inflammatory, and neoplastic tissues

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


LMP1

Epstein Barr Virus Latency Membrane Protein 1 Immunostain, Technical Component Only

Clinical Information: The latent membrane protein 1 (LMP-1) oncogene of Epstein-Barr virus (EBV) is believed to contribute to the development of many EBV-associated tumors. This antibody may be useful in the diagnosis of reactive and neoplastic lymphoproliferative and plasma cell proliferative disorders.

Useful For: Identification of Epstein Barr virus infection in normal, inflammatory, and neoplastic tissues

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Epstein-Barr Virus (EBV) Antibody Profile, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be recognized, however, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test; eg, MONOS / Infectious Mononucleosis, Rapid Test, Serum), which usually appear within the first 3 weeks of illness but then decline rapidly within a few weeks. The heterophile antibody, however, fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody-negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in a series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected but the heterophile antibody is not detected, an evaluation of the EBV-specific antibody profile (eg, EBV viral capsid antigen: VCA IgM, EBV VCA IgG, and EBV nuclear antigen: EBNA) may be useful. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection have been recognized for several years, including African-type Burkitt lymphoma and nasopharyngeal carcinoma. EBV infection may also cause lymphoproliferative syndromes, especially in patients who have undergone renal or bone marrow transplantation and in those who have AIDS.

Useful For: Diagnosing infectious mononucleosis when a mononucleosis screening procedure is negative and infectious mononucleosis or a complication of Epstein-Barr virus infection is suspected. This assay is not intended for viral isolation or identification.

Interpretation: The test has 3 components: viral capsid antigen (VCA) IgG, VCA IgM, and Epstein-Barr nuclear antigen (EBNA). Presence of VCA IgM antibodies indicates recent primary infection with Epstein-Barr virus (EBV). The presence of VCA IgG antibodies indicates infection sometime in the past. Antibodies to EBNA develop 6 to 8 weeks after primary infection and are detectable for life. Over 90% of the normal adult population has IgG class antibodies to VCA and EBNA. Few patients who have been infected with EBV will fail to develop antibodies to the EBNA (approximately 5%-10%). Possible results VCA IgG VCA IgM EBNA IgG Interpretation - - - No previous exposure + + - Recent infection + - + Past infection + - See note* + + + Past infection *Results indicate infection with EBV at some time (VCA IgG positive). However, the time of the infection cannot be predicted (ie, recent or past) since antibodies to EBNA usually develop after primary infection (recent) or, alternatively, approximately 5% to 10% of patients with EBV never develop antibodies to EBNA (past).

Reference Values:
Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgM ANTIBODY
Negative

Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgG ANTIBODY
Negative

EPSTEIN-BARR NUCLEAR ANTIGEN (EBNA) ANTIBODIES
Negative

**Clinical Information:** Epstein-Barr virus (EBV) plays a pathogenic role in a variety of disease states, including infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma, B-cell lymphomas in patients with congenital or acquired immunodeficiency, and some cases of classical Hodgkin lymphoma.

**Useful For:** Detection of Epstein-Barr virus (EBV)-encoded RNA (EBER) in the diagnosis of EBV-associated conditions

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Epstein-Barr Virus (EBV), IgG Antibody to Early Antigen, Serum**

**Clinical Information:** Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be recognized, however, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test; eg, MONOS / Infectious Mononucleosis Rapid Test, Serum). Heterophile antibodies usually appear within the first 3 weeks of illness but decline rapidly within a few weeks. However, this heterophile antibody fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in one series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected but the heterophile antibody is not detected, an evaluation of EBV-specific antibodies (eg, IgM and IgG antibodies to EBV viral capsid antigen: VCA) and antibodies to EBV nuclear antigen (EBNA) may be useful. The EBV EIA tests that detect antibodies to the EBV VCA and early antigen (EA) are more sensitive than heterophile antibody tests. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection include African-type Burkitt lymphoma and nasopharyngeal carcinoma (NPC). EBV infection may also cause lymphoproliferative syndromes, especially in patients with AIDS and in patients who have undergone renal or bone marrow transplantation. Using immunofluorescent staining techniques, 2 patterns of EA are seen, 1) diffuse staining of both cytoplasm and nucleus (early antigen-diffuse: EA-D) and 2) cytoplasmic or early antigen restricted (EA-R). Antibodies responsible for the diffuse staining pattern (EA-D) are seen in infectious mononucleosis and NPC, and are measured in this assay.

**Useful For:** A third-order test in the diagnosis of infectious mononucleosis, especially in situations when initial testing results (heterophile antibody test) are negative and follow-up testing (viral capsid antigen: VCA IgG, VCA IgM, and Epstein-Barr nuclear antigen) yields inconclusive results aiding in the diagnosis of type 2 or type 3 nasopharyngeal carcinoma

**Interpretation:** Generally, this antibody can only be detected during active Epstein-Barr virus (EBV) infection, such as in patients with infectious mononucleosis. Clinical studies have indicated that...
patients who have chronic active or reactivated EBV infection commonly have elevated levels of IgG-class antibodies to the EA of EBV. IgG antibody specific for the diffuse early antigen of EBV is often found in patients with nasopharyngeal carcinoma (NPC). Of patients with type 2 or 3 NPC (World Health Organization classification), 94% and 83% respectively, have positive-antibody responses to EA. Only 35% of patients with type 1 NPC have a positive response. The specificity of the test is such that 82% to 91% of healthy blood donor controls and patients who do not have NPC have negative responses (9%-18% false-positives). Although this level of specificity is useful for diagnostic purposes, the false-positive rate indicates that the test is not useful for NPC screening.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References:

EBV
81239

Epstein-Barr Virus (EBV), Molecular Detection, PCR, Varies

Clinical Information: Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, Burkitt lymphoma, and in Southern China, nasopharyngeal carcinoma. EBV-associated central nervous system (CNS) disease is most commonly associated with primary CNS lymphoma in patients with AIDS. In addition, CNS infection associated with the detection of EBV DNA can be seen in immunocompetent patients.

Useful For: Rapid qualitative detection of Epstein-Barr virus (EBV) DNA in specimens for laboratory diagnosis of disease due to this virus

Interpretation: Detection of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid (CSF) supports the clinical diagnosis of central nervous system (CNS) disease due to the virus. EBV DNA is not detected in CSF from patients without CNS disease caused by this virus.

Reference Values:
Negative

Clinical References:

EBVQU
65754

Epstein-Barr Virus DNA Detection and Quantification, Plasma

Clinical Information: Primary infection with Epstein-Barr virus (EBV), a DNA virus in the Herpesviridae family, may cause infectious mononucleosis resulting in a benign lymphoproliferative condition characterized by fever, fatigue, sore throat, and lymphadenopathy. Infection occurs early in life, and by 10 years of age, 70% to 90% of children have been infected with this virus. Usually, infection in
children is asymptomatic or mild and may be associated with minor illnesses such as upper respiratory tract infection, pharyngitis, tonsillitis, bronchitis, and otitis media. The target cell for EBV infection is the B-lymphocyte. Immunocompromised individuals lacking antibody to EBV are at risk for acute EBV infection that may cause lymphoproliferative disorders in organ transplant recipients (posttransplant lymphoproliferative disorders [PTLD]) and AIDS-related lymphoma. The incidence of PTLD ranges from 1% for renal transplant recipients to as high as 9% for heart/lung transplants and 12% for pancreas transplant patients. EBV DNA can be detected in the blood of patients with this viral infection, and increasing serial levels of EBV DNA in plasma have been shown to correlate highly with subsequent (in 3-4 months) development of PTLD in susceptible patients. Organ transplant recipients who are sero-negative (at risk for primary EBV infection) for EBV (most often children) who receive antilymphocyte globulin for induction immunosuppression and OKT-3 treatment for early organ rejection are at highest risk for developing PTLD when compared to immunologically normal individuals with prior EBV infection.

**Useful For:**

- Diagnosis of EBV-associated infectious mononucleosis in individuals with equivocal or discordant Epstein-Barr virus (EBV) serologic marker test results
- Diagnosis of posttransplant lymphoproliferative disorders (PTLD), especially in EBV-seronegative organ transplant recipients receiving antilymphocyte globulin for induction immunosuppression and OKT-3 treatment for early organ rejection
- Monitoring progression of EBV-associated PTLD in organ transplant recipients

**Interpretation:**

The quantification range of this assay is 100 to 5,000,000 IU/mL (or 2.00-6.70 log IU/mL), with a limit of detection (based on a 95% detection rate) at 45 IU/mL (1.65 log IU/mL). Increasing levels of Epstein-Barr virus (EBV) DNA in serial plasma specimens of a given organ transplant recipient may indicate possible development of posttransplant lymphoproliferative disorder (PTLD). An "Undected" result indicates that EBV DNA is not detected in the plasma specimen (see Cautions). If clinically indicated, repeat testing in 1 to 2 months is recommended. A result of "<100 IU/mL" indicates that the EBV DNA level present in the plasma specimen is below 100 IU/mL (or 2.00 log IU/mL), and the assay cannot accurately quantify the EBV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the EBV DNA level (ie, viral load) present in the plasma specimen. A result of ">5,000,000 IU/mL" indicates that the EBV DNA level present in the plasma specimen is above 5,000,000 IU/mL (6.70 log IU/mL), and this assay cannot accurately quantify the EBV DNA present above this level. An "Inconclusive" result indicates that the presence or absence of EBV DNA in the plasma specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to PCR inhibition or presence of interfering substance. Submission of a new specimen for testing is recommended if clinically indicated.

**Reference Values:**

Undetected

**Clinical References:**


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**ERG Immunostain, Technical Component Only**

**Clinical Information:**

ETS-related gene (ERG) is a member of the erythroblast transformation specific (ETS) family of transcription factors. Expression of ERG is observed in prostate cancers where the TMPRSS2-ERG gene rearrangement has occurred.

**Useful For:**

Identification of erythroblast transformation specific (ETS)-related gene (ERG) protein expression.
**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Erythrocytosis Evaluation, Whole Blood**

**Clinical Information:** Erythrocytosis (polycythemia) is identified by a sustained increase in hemoglobin or hematocrit. An isolated increase in red blood cells (RBC) count (in the absence of chronic phlebotomy or coincident iron deficiency) may occur in thalassemia or other causes and does not indicate erythrocytosis. Erythrocytosis may occur as a primary disorder, due to an intrinsic defect of bone marrow stem cells, or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be present. It is important to differentiate polycythemia vera (PV) from heritable causes of erythrocytosis, the latter of which can be passed to progeny but do not carry the risks of clonal evolution or marrow fibrosis associated with PV. The most common cause of hereditary erythrocytosis is the presence of high-oxygen-affinity (HOA) hemoglobin. A subset of hemoglobins with increased oxygen (O2) affinity result in clinically evident erythrocytosis caused by decreased O2 unloading at the tissue level. Many are asymptomatic; however some patients have recurrent headaches, dizziness, fatigue and restless legs. A minor subset of patients has thrombotic episodes. Affected individuals can be plethoric and many are misclassified as polycythemia vera. The oxygen dissociation curve is left-shifted (p50 values are decreased). Changes to the amino acid sequence of the hemoglobin molecule may distort the protein structure, affecting O2 transport or unloading and the binding of 2,3-bisphosphoglyceric acid (2,3-BPG). 2,3-BPG stabilizes the deoxygenated state of hemoglobin. Therefore a decrease in the 2,3-BPG concentration results in greater O2 affinity of the normal hemoglobin molecule. A few cases of erythrocytosis have been associated with a reduction in 2,3-BPG formation. This is most commonly due to variants in the encoding enzyme, bisphosphoglycerate mutase (BPGM). Truncating variants in the erythropoietin receptor gene, EPOR, have been shown to be a cause of the autosomal dominant primary familial and congenital polycythemia (PFCP)(OMIM 133100). In addition, oxygen sensing pathway variants, EPAS1(HIF2A)(OMIM 611783); EGLN1(PHD2)(OMIM 609820), and VHL (OMIM 263400) cause hereditary erythrocytosis and a subset are associated with pheochromocytoma and paragangliomas. All have shown an autosomal dominant pattern of inheritance, except VHL-associated erythrocytosis, which is an autosomal recessive disorder. Homozygous VHL R200W alterations have been shown to be causative of Chuvash polycythemia, an endemic heritable erythrocytic disorder first described in Russia but subsequently found in other ethnic groups. The prevalence of causative variants in EPOR and the oxygen sensing pathway genes is unknown, but in our experience they are less prevalent than genetic variants that cause HOA hemoglobin variants, and much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful for evaluating these disorders. Initial JAK2 V617F alteration testing and serum EPO levels are important with p50 results further stratifying JAK2-negative cases. Importantly, a significant subset of HOA hemoglobin variants can be electrophoretically silent on multiple routine screening platforms; however, most if not all of HOAs can be identified with addition of the mass spectrometry method. Our extensive experience with these disorders allows an economical,
Useful For: Definitive, comprehensive, and economical evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased hemoglobin or hematocrit.

Interpretation: The evaluation includes testing for a hemoglobinopathy and oxygen (O2) affinity of the hemoglobin molecule. An increase in O2 affinity is demonstrated by a shift to the left in the O2 dissociation curve (decreased p50 result). Reflex testing for EPOR, EGLN1 (PHD2), EPAS1 (HIF2a), VHL, and BPGM will be performed as needed. A hematopathologist expert in these disorders will evaluate the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values: Definitive results and an interpretive report will be provided.

dominant pattern of inheritance, except VHL-associated erythrocytosis, which is an autosomal recessive disorder. Homozygous VHL R200W alterations have been shown to be causative of Chuvash polycythemia, an endemic heritable erythrocytic disorder first described in Russia but subsequently found in other ethnic groups. The prevalence of causative variants in EPOR and the oxygen sensing pathway genes is unknown, but in our experience they are less prevalent than genetic variants that cause HOA hemoglobin variants, and much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful for evaluating these disorders. Initial JAK2 V617F alteration testing and serum EPO levels are important with p50 results further stratifying JAK2-negative cases. Importantly, a significant subset of HOA hemoglobin variants can be electrophoretically silent on multiple routine screening platforms; however, most if not all of HOAs can be identified with addition of the mass spectrometry method. Our extensive experience with these disorders allows an economical, comprehensive evaluation with high sensitivity.

Useful For: Interpretation of results for the evaluation of erythrocytosis Definitive, comprehensive, and economical evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased hemoglobin or hematocrit

Interpretation: The evaluation includes testing for a hemoglobinopathy and oxygen (O2) affinity of the hemoglobin molecule. An increase in O2 affinity is demonstrated by a shift to the left in the O2 dissociation curve (decreased p50 result). Reflex testing for EPOR, EGLN1 (PHD2), EPAS1 (HIF2a), VHL, and BPGM will be performed as needed. A hematopathologist expert in these disorders will evaluate the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Only orderable as part of a profile. For more information see REVE1 / Erythrocytosis Evaluation, Whole Blood.

Clinical References:
An interpretive report will be provided.


### Erythropoietin Receptor (EPOR) Gene, Exon 8 Sequencing, Whole Blood

**Clinical Information:** Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paranganglioma formation. It is caused by variants in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new alterations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing alterations is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal level to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is Current as of June 14, 2021 12:13 pm CDT
encoded by the PHD2 (EGLN1) gene. Genetic variants resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known alterations have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels and normal p50 values (see Table).

**Useful For:** Assessing EPOR in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** An interpretive report will be provided as a part of the HEMP / Hereditary Erythrocytosis Mutations, Whole Blood, and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

An interpretive report will be provided.

**Clinical References:**

**Clinical Information:**
Erythropoietin (EPO), a large (193 amino acid residue) glycoprotein hormone secreted by the kidney, regulates red blood cell (RBC) production. Normally, EPO levels vary inversely with hematocrit. Hypoxia stimulates EPO release, which, in turn, stimulates bone marrow erythrocyte production. High blood levels of RBC, hemoglobin, hematocrit, or oxygen suppress the release of EPO. Primary polycythemia (polycythemia vera) is a neoplastic (clonal) blood disorder characterized by autonomous production of hematopoietic cells. Increased RBCs result in compensatory suppression of EPO levels. Findings consistent with polycythemia vera include hemoglobin greater than 18.5 g/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegalay, and erythromelalgia (dysesthesia and erythema involving the distal extremities). Secondary polycythemias may either be due to an appropriate or an inappropriate increase in red cell mass. Appropriate secondary polycythemias (eg, high-altitude living and pulmonary disease) are characterized by hypoxia and a compensatory increase in red cell mass. EPO production is increased in an attempt to increase the delivery of oxygen by increasing the number of oxygen-carrying RBCs. Some tumors secrete EPO or EPO-like proteins; examples include tumors of the kidney, liver, lung, and brain. Such increases result in
inappropriate secondary polycythemias. Abnormal EPO levels also may be seen in renal failure. The majority of EPO production is in the kidneys. Therefore, chronic kidney failure may result in decreased EPO production and, subsequently, anemia. In addition to the kidneys, the liver also produces a small amount of EPO. Thus, patients who are anephric have a residual amount of EPO produced by the liver. Patients in chronic kidney failure, as well as patients with anemia due to a variety of other causes including chemotherapy, HIV/AIDS, and some hematologic disorders, may be candidates for treatment with recombinant human EPO. Recombinant EPO compounds used to treat anemia include epoetin alpha and darbepoetin. Epoetin alpha is a 165 amino acid glycoprotein produced in mammalian cells and has an identical amino acid sequence to natural human EPO. It has 3 oligosaccharide chains and a molecular mass of 30.4 kDa. Darbepoetin alpha is a 165 amino acid glycoprotein that is also produced in mammalian cells. It has 2 additional N-linked oligosaccharide chains and a molecular mass of 37 kDa. There are no specific assays for measuring recombinant EPO compounds. Drug levels can only be roughly estimated from the cross reactivity of the compounds in EPO assays. According to in-house studies, epoetin and darbepoetin show approximately 58% and 36% cross-reactivity, respectively, in the EPO assay.

**Useful For:** An aid in distinguishing between primary and secondary polycythemia Differentiating between appropriate secondary polycythemia (eg, high-altitude living, pulmonary disease, tobacco use) and inappropriate secondary polycythemia (eg, tumors) Identifying candidates for erythropoietin (EPO) replacement therapy (eg, those with chronic renal failure) Evaluating patients undergoing EPO replacement therapy who demonstrate an inadequate hematopoietic response

**Interpretation:** In the appropriate clinical setting (eg, confirmed elevation of hemoglobin >18.5 g/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia), polycythemia vera is unlikely when erythropoietin (EPO) levels are elevated but is likely when EPO levels are suppressed. EPO levels are also increased in patients with anemia of bone marrow failure, iron deficiency, or thalassemia. Patients, who have either a poor or no erythropoietic response to EPO therapy, but high-normal or high EPO levels, may have additional, unrecognized causes for their anemia. If no contributing factors can be identified after adequate further study, the possibility that the patient may have developed EPO-antibodies should be considered. This can be a serious clinical situation that can result in red cell aplasia and should prompt expeditious referral to hematologists or immunologists skilled in diagnosing and treating this disorder.

**Reference Values:**
2.6-18.5 mIU/mL

**Clinical References:**

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**Escherichia coli O157:H7 Culture, Feces**

**Clinical Information:** Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Shiga toxin-producing Escherichia coli (STEC) are E coli strains capable of producing Shiga toxin, which can result in diarrhea that can be bloody. The incubation period between exposure and symptom onset is 1 to 9 days. Hemolytic-uremic syndrome
(HUS) is a systemic complication of STEC infection and is characterized by renal failure, microangiopathic hemolytic anemia, and nonimmune thrombocytopenia. HUS complicates approximately 15% of STEC infections in children younger than 10 years and 6% to 9% overall. Treatment of STEC infection consists of supportive care. Antibiotic therapy is generally not beneficial in patients with STEC infection and has been associated with development of HUS in some studies. Thus, when STEC is clinically suspected, antibiotics should be withheld. Antiperistaltic agents also increase the risk of systemic complications and should be avoided.

**Useful For:** Determining whether Escherichia coli O157:H7 may be the cause of diarrhea Reflexive testing for Shiga toxin and/or E coli O157:H7 nucleic acid amplification test-positive feces This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

**Interpretation:** The growth of Escherichia coli O157:H7 identifies a potential cause of diarrhea.

**Reference Values:**
No growth of pathogen

**Clinical References:**

### Estradiol Free, Serum (includes Estradiol and SHBG)

**Reference Values:**
Estradiol, Serum MS
Units: pg/mL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Levels are markedly elevated at birth and fall rapidly during the first week to prepubertal values of &lt;15.</td>
</tr>
<tr>
<td>Males &lt;6 m</td>
<td>Levels increase to 10 - 32 between 30 and 60 days, then decline to prepubertal levels of &lt;15 by six months.</td>
</tr>
<tr>
<td>Females &lt;1 y</td>
<td>Levels increase to 5.0 - 50 between 30 and 60 days, then decline to prepubertal levels of &lt;15 during the first year.</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Adult Males</td>
<td>8.0 - 35</td>
</tr>
<tr>
<td>Adult Females</td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>30 - 100</td>
</tr>
<tr>
<td>Luteal</td>
<td>70 - 300</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Free Estradiol, Percent
Units: %

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>1.7 - 5.4</td>
</tr>
<tr>
<td>Adult Females</td>
<td>1.6 - 3.6</td>
</tr>
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</table>

FFES 91215
Free Estradiol, Serum
Units: pg/mL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>0.2 - 1.5</td>
</tr>
<tr>
<td>Adult Females</td>
<td>0.6 - 7.1</td>
</tr>
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</table>

Sex Hormone Binding Globulin
Units: nmol/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (1 - 23m)</td>
<td>60.0 - 252.0</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>72.0 - 220.0</td>
</tr>
<tr>
<td>Pubertal</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>16.0 - 100.0</td>
</tr>
<tr>
<td>Females</td>
<td>36.0 - 125.0</td>
</tr>
<tr>
<td>Adult Males</td>
<td></td>
</tr>
<tr>
<td>20 - 49 y</td>
<td>16.5 - 55.9</td>
</tr>
<tr>
<td>&gt;49y</td>
<td>19.3 - 76.4</td>
</tr>
<tr>
<td>Adult Females</td>
<td></td>
</tr>
<tr>
<td>20 – 49y</td>
<td>24.6 - 122.0</td>
</tr>
<tr>
<td>&gt;49y</td>
<td>17.3 - 125.0</td>
</tr>
</tbody>
</table>

Estradiol, Rapid, Immunoassay, Serum

**Clinical Information:** Estrogens are responsible for the development and maintenance of female sex organs and female secondary sex characteristics. In conjunction with progesterone, they participate in regulation of the menstrual cycle, breast and uterine growth, and in the maintenance of pregnancy. Estrogens affect calcium homeostasis and have a beneficial effect on bone mass. They decrease bone resorption and, in prepubertal girls, estrogen accelerates linear bone growth. Long-term estrogen depletion is associated with loss of bone mineral content, an increase in stress fractures, and postmenopausal osteoporosis. The 3 most biologically active estrogens in order of potency are estrone (E1), estradiol (E2), and estriol (E3). Estrogens are produced primarily in the ovary (follicle, corpus luteum), but small quantities are also formed in the testes and in the adrenal cortex. During pregnancy, estrogens are mainly formed in the placenta. About 98% of estradiol is bound to transport proteins (sex hormone-binding globulin: SHBG) and albumin. Estrogen secretion is biphasic during the menstrual cycle. The determination of estradiol is utilized clinically in the elucidation of fertility disorders in the hypothalamus-pituitary-gonad axis, gynecomastia, estrogen-producing ovarian and testicular tumors, and in hyperplasia of the adrenal cortex. Additional clinical indications are the monitoring of fertility therapy and determining the time of ovulation within the framework of in vitro fertilization (IVF). The laboratory plays an important role in the process of ovulation induction. The principle involves administration of gonadotropins to stimulate follicular growth, followed by human chorionic gonadotropin (hCG) to stimulate ovulation follicular maturation. Clinical, laboratory, and ultrasound monitoring of the treatment cycle is necessary to identify the dose and length of therapy, determine when or whether to administer hCG, and obtain an adequate ovulatory response while avoiding hyperstimulation. For other clinical indications, order EEST / Estradiol, Serum.

**Useful For:** Rapid assessment of ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) Establishing time of ovulation and optimal time for conception

**Interpretation:** Optimal time for conception is within 48 to 72 hours following the midcycle estradiol peak. Serial specimens must be drawn over several days to evaluate baseline and peak estradiol levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization (IVF) studies, low levels before stimulation are critical, as higher values often are
associated with poor stimulation cycles. Before final human chorionic gonadotropin (hCG) stimulation at mid-IVF cycle, estradiol concentrations above 2,000 to 3,000 pg/mL are considered by some IVF specialists to be indicative of an increased likelihood of ovarian hyperstimulation and it may be advisable to consider withholding further hCG stimulation. Estradiol (E2) concentrations below 200 pg/mL following midcycle stimulation (hCG or follicle-stimulating hormone: FSH) are associated with very low pregnancy success rates. E2 concentrations change during the menstrual cycle, as follows:

- less than 50 pg/mL before midfollicular phase
- 250 to 500 pg/mL midcycle peak as the follicle matures
- Abrupt decrease after ovulation
- 125 pg/mL peak during the luteal phase

Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be within the normal range.

**Reference Values:**

Males: 10-40 pg/mL

Females
- Premenopausal: 15-350 pg/mL*
- Postmenopausal: <10 pg/mL

*Estradiol concentrations vary widely throughout the menstrual cycle

The limit of quantitation for estradiol measured by immunoassay is 25 pg/mL. Mass spectrometry is the preferred method for measurement of low serum estradiol concentrations in children, males and postmenopausal females (EEST / Estradiol, Serum).

**Clinical References:**


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**Estradiol, Serum**

**Clinical Information:** Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone (LH)/follicle stimulating hormone (FSH) surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and, thereafter, decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-menorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. See Steroid Pathways in Special
Useful For: All applications that require moderately sensitive measurement of estradiol. Evaluation of hypogonadism and oligo-amenorrhea in females. Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization). In conjunction with luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women. Evaluation of feminization, including gynecomastia, in males. Diagnosis of estrogen-producing neoplasms in males and, to a lesser degree, females. As part of the diagnosis and workup of precocious and delayed puberty in females, and, to a lesser degree, males. As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency). As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men. Monitoring low-dose female hormone replacement therapy in postmenopausal women. Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy).

Interpretation: Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmune polyglandular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately "normal," a diagnosis of hypogonadotrophic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further workup is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging.

Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone: E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further workup is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. E2 levels change during the menstrual cycle, as follows: Post-menses, levels may be as low as 15 pg/mL. Levels then rise during the follicular phase to a preovulatory peak, typically in the 300+ pg/mL range. Levels fall in the luteal phase. Menses typically occur when E2 levels are in the 50 to 100 pg/mL range. E2 analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be drawn over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation, are critical, as higher values often are associated with poor stimulation cycles. Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women. LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the workup should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization. Obesity with increased tissue production of E1 and E2 clearance in liver disease. Estrogen producing tumors. Estrogen ingestion.
be associated with feminization or gynecomastia, if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the workup for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels below 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo-precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallmann syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. See Steroid Pathways in Special Instructions.

Reference Values:

<table>
<thead>
<tr>
<th>Tanner Stages#</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-13 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>12.1 years</td>
<td>Undetectable-16 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>Undetectable-26 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1 years</td>
<td>Undetectable-38 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-40 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tanner Stages#</th>
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<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-20 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>Undetectable-24 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>11.6 years</td>
<td>Undetectable-60 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>12.3 years</td>
<td>15-85 pg/mL</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT
Stage V 14.5 years 15-350 pg/mL** #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data, and on our data for young adults. ADULTS Males: 10-40 pg/mL. Females Premenopausal: 15-350 pg/mL** Postmenopausal: **E2 levels vary widely through the menstrual cycle. Conversion factor E2: pg/mL x 3.676=pmol/L (molecular weight=272) For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html


Estriol, Unconjugated, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. There are 3 major biologically active estrogens in humans: estrone (E1), estradiol (E2), and estriol (E3). Like all members of the steroid hormone family, they diffuse into cells and bind to specific nuclear receptors, which in turn alter gene transcription in a tissue specific manner. E2 is the most potent natural human estrogen, closely followed by E1, while E3 possess only 20% of the E2 affinity for the estrogen receptor. In men and nonpregnant women, E1 and E2 are formed from the androgenic steroids androstenedione and testosterone, respectively. E3 is derived largely through conversion of E2, and to a lesser degree from 16a-metabolites of E1. E2 and E1 can also be converted into each other, and both can be inactivated via hydroxylation and conjugation. During pregnancy E3 becomes the dominant estrogen. The fetal adrenal gland secretes dehydroepiandrosterone-sulfate (DHEAS), which is converted to E3 in the placenta and diffuses into the maternal circulation. The half-life of unconjugated E3 (uE3) in the maternal blood system is 20 to 30 minutes since the maternal liver quickly conjugates E3 to make it more water soluble for urinary excretion. E3 levels increase throughout the course of pregnancy, peaking at term. Decreased second trimester uE3 has been shown to be a marker for Down and trisomy-18 syndromes. uE3 is a part of multiple marker prenatal biochemical screening, together with alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and inhibin-A measurements. Low levels of uE3 also have been associated with pregnancy loss, Smith-Lemli-Opitz syndrome (defect in cholesterol biosynthesis), X-linked ichthyosis and contiguous gene syndrome (placental sulfatase deficiency disorders), aromatase deficiency, and primary or secondary fetal adrenal insufficiency.

Useful For: A part of second trimester or cross-trimester biochemical screening for Down syndrome and trisomy 18 syndrome A marker of fetal demise An adjunct biomarker in the prenatal diagnosis of disorders of fetal steroid metabolism, including Smith-Lemli-Opitz syndrome (SLO)(3-4), and X-linked ichthyosis (placental sulfatase deficiency disorders) Evaluating primary or secondary fetal adrenal insufficiency after excluding other rare single gene defects, including aromatase deficiency, 17 alpha-hydroxylase deficiency and/or various forms of congenital adrenal hyperplasia
Interpretation: In second trimester maternal serum screening (QUAD), unconjugated E3 (uE3) forms part of a complex, multivariate risk calculation formula, using maternal age, gestational stage, and other demographic information, in addition to the results of the biochemical markers, for Down syndrome and trisomy 18 risk calculation. A serum uE3 <0.15 multiples of the gestational age median in women, who otherwise screen negative in the quad test, can indicate Smith-Lemli-Opitz syndrome and X-linked ichthyosis. A low uE3 level can indicate the possibility of aromatase deficiency, congenital adrenal hyperplasia, primary or secondary (including maternal corticosteroid therapy) fetal adrenal insufficiency and/or fetal demise.

Reference Values:
Males: <0.07 ng/mL
Females: <0.08 ng/mL

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

Clinical References:

ESR1 65414

Estrogen Receptor 1 (ESR1) Mutation Analysis, Tumor

Clinical Information: The estrogen receptor 1 (ESR1) gene encodes an estrogen receptor that regulates cell growth through activation of downstream signaling pathways upon binding of estrogen. Tumors demonstrating estrogen receptor expression (ER-positive) are candidates for endocrine therapy such as selective estrogen receptor modulators (SERM) and aromatase inhibitors. ESR1 mutations are rarely observed in primary tumors; however, mutations in the ligand-binding domain of ESR1 have been reported at a higher frequency in ER-positive metastatic breast tumors. Preclinical data suggests that ESR1 mutations mitigate resistance to aromatase inhibitors and decrease sensitivity to SERMs and estrogen-receptor downregulators. Studies also suggest that ESR1 mutations are an independent indicator of poor prognosis. This test assesses for somatic mutations in the ligand-binding domain of the ESR1 gene associated with acquired resistance to endocrine therapy (ie, aromatase inhibitors) in patients with ER-positive metastatic breast cancer.

Useful For: Assisting in the clinical management of patients with metastatic breast cancer by identifying tumors with evolving resistance to endocrine therapy. Stratifying prognosis of metastatic breast cancer. This test is not useful for hematological malignancies.

Interpretation: An interpretative report will be provided.

Reference Values: An interpretative report will be provided.

Clinical References:
**ERBE1 71485**

**Estrogen Receptor Beta-1 Immunostain, Technical Component Only**

**Clinical Information:** This test is intended to identify the presence of estrogen receptor beta 1 (ER-beta 1) protein. ER-beta 1 is a member of the nuclear receptor superfamily of transcription factors and is the product of the ESR2 gene on chromosome 14q22-24. Unlike ER-alpha, ER-beta 1 is highly expressed in normal breast epithelium but expression is reduced in many precancerous and cancerous breast tumors. ER-beta 1 is expressed in 30% to 40% of triple negative breast cancers and is associated with improved outcomes in ER-alpha positive tamoxifen treated patients.

**Useful For:** Detection of estrogen receptor-beta 1 protein levels in cancer, including triple-negative breast cancer

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**ESTR 70427**

**Estrogen Receptor Immunostain, Technical Component Only**

**Clinical Information:** Estrogen receptor alpha protein expression is limited to normal and neoplastic tissues related to the reproductive system (breast, cervix, endometrium, uterus, ovary, and prostate).

**Useful For:** Qualitative detection of estrogen receptor alpha protein in a diagnostic setting

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Estrogen/Progesterone Receptor, Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** The steroid hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), are commonly used in the management of women with breast cancer. ER and PR status provide an indication of prognosis and of the potential benefit from hormonal therapy. Generally, ER/PR-positive tumors are more likely to respond to endocrine therapy and have a better prognosis, stage-for-stage, than receptor-negative tumors. While the test can be performed on any formalin-fixed, paraffin-embedded tissue, it is infrequently used for non-breast cancer specimens.

**Useful For:** Guiding decisions on hormonal therapy in patients with breast carcinomas. This test is not useful for cases of lobular carcinoma in situ.

**Interpretation:** Immunoperoxidase-stained slides are examined microscopically by the consulting anatomic pathologist and interpreted as negative (<1% reactive cells), or positive. The percent of reactive cells is provided in the report.

**Reference Values:**
- Negative: <1% reactive cells
- Positive: > or =1% reactive cells

**Clinical References:**

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**Estrogens, Estrone (E1) and Estradiol (E2), Fractionated, Serum**

**Clinical Information:** Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, non-gender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then gradually increase again until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of...
E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment.

**Useful For:** Simultaneous high-sensitivity determination of serum estrone and estradiol levels
- Situations requiring either higher sensitivity estradiol measurement, estrone measurement, or both, including - As part of the diagnosis and workup of precocious and delayed puberty in females and, to a lesser degree, males - As part of the diagnosis and workup of suspected disorders of sex steroid metabolism, eg, aromatase deficiency and 17 alpha-hydroxylase deficiency - As an adjunct to clinical assessment, imaging studies, and bone mineral density measurement in the fracture risk assessment of postmenopausal women and, to a lesser degree, older men - Monitoring low-dose female hormone replacement therapy in postmenopausal women - Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)
- Applications that require moderately sensitive measurement of estradiol including:
  - Evaluation of hypogonadism and oligo-amenorrhea in females - Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) In conjunction with luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women Evaluation of feminization, including gynecomastia, in males Diagnosis of estrogen-producing neoplasms in males, and, to a lesser degree, females

**Interpretation:** Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmune polyglandular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately "normal," a diagnosis of hypogonadotropic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further work-up is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging. Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone: E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. E2 analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be drawn over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation are critical, as higher values often are associated with poor stimulation cycles. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women. LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL.

Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the workup should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include:
- High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2
due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal male E1 and E2 levels also may be associated with feminization or gynecomastia, if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone (GnRH) stimulation test remains the central part of the workup for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels less than 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly, in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotropic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high.

Reference Values:

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<td>Stage III</td>
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<tr>
<td>Stage IV</td>
<td>15.1 years</td>
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<td>Stage V</td>
<td>18 years</td>
<td>10-60 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females</td>
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**Stage V**  
14.5 years  
17-200 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature,(1,2) cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-60 pg/mL Females Premenopausal: 17-200 pg/mL Postmenopausal: 7-40 pg/mL Conversion factor E1: pg/mL x 3.704=pmol/L (molecular weight=270) ESTRADIOL (E2) CHILDREN* 1-14 days: Estradiol levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males

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<td>Undetectable-26 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
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</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-40 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females</td>
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<td>Stage V</td>
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<td>15-350 pg/mL** #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. ** The reference ranges for children are based on the published literature,(1,2) cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-40 pg/mL Females Premenopausal: 15-350 pg/mL** Postmenopausal: **E2 levels vary widely through the menstrual cycle. Conversion factor E2: pg/mL x 3.676=pmol/L (molecular weight=272) For SI unit Reference Values, see <a href="https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html">https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html</a></td>
</tr>
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</table>

**Clinical References:** 1. Elmlinger MW, Kuhnel W, Ranke MB: Reference ranges for serum concentrations of lutropin (LH), follitropin (FSH), estradiol (E2), prolactin, progesterone, sex

E1
81418

**Estrone, Serum**

**Clinical Information:** Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25-5 times the biological potency of E1. E2 circulates at 1.5-4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/ follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays or simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. See Steroid Pathways in Special Instructions.

**Useful For:** As part of the diagnosis and workup of precocious and delayed puberty in females and, to a lesser degree, males As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency) As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men Monitoring low-dose female hormone replacement therapy in postmenopausal women Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)
**Interpretation:** Irregular or absent menstrual periods with normal or high estradiol (E2) levels (and often high estrone: E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, luteinizing hormone/follicle-stimulating hormone (LH/FSH) should be within the normal range, and E2 levels should ideally be higher than E1 levels. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal male E1 and E2 levels also may be associated with feminization or gynecomastia if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the work-up for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels less than 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotropic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. See Steroid Pathways in Special Instructions.

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Stage V 18 years 10-60 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females

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Ethanol, Blood

Clinical Information: Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL.

Useful For: Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication
**Interpretation:** The presence of ethanol in blood at concentrations above 30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels above 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level above 80 mg/dL (>0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level of 400 mg/dL (> or =0.4%) or higher may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug, and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level above 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

**Reference Values:**
Not detected (Positive results are quantified.)
- Limit of detection: 10 mg/dL (0.01 g/dL)
- Legal limit of intoxication is 80 mg/dL (0.08 g/dL).
- Toxic concentration is dependent upon individual usage history.
- Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)


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**Ethanol, Chain of Custody, Blood**

**Clinical Information:** Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL. Chain of custody is required whenever the results of testing could be used in a court of law. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** All testing is performed under strict chain of custody Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication

**Interpretation:** The presence of ethanol in blood at concentrations greater than 30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels above 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level above 80 mg/dL (>0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level of 400 mg/dL (> or =0.4%) or more may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug, and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level above 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

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Not detected (Positive results are quantified.)
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Legal limit of intoxication is 80 mg/dL (0.08 g/dL). Toxic concentration is dependent upon individual usage history. Potentially lethal concentration: ≥ 400 mg/dL (0.4 g/dL)


### Ethosuximide, Serum

**Clinical Information:** Ethosuximide (Zarontin) is used in the treatment of absence (petit mal) epilepsy in adults and children 3 years of age and older. Ethosuximide is almost completely absorbed from the gastrointestinal tract, reaching a peak plasma concentration in 1 to 4 hours following oral administration. Approximately 10% to 20% of the drug is excreted unchanged in the urine; the remainder is metabolized by hepatic microsomal enzymes. The volume of distribution of ethosuximide is approximately 0.7 L/kg, and its half-life is 17-56 hours (adult) and 30 hours (pediatric). Minimal ethosuximide circulating in the blood is bound to protein (approximately 22%). Ethosuximide produces a barbiturate-like toxicity, characterized by central nervous system and respiratory depression, nausea, and vomiting, when the blood level is greater than 120 mcg/mL.

**Useful For:** Monitoring ethosuximide therapy Determining compliance Assessing ethosuximide toxicity

**Interpretation:** Dosage is guided by blood levels; the therapeutic range for ethosuximide is 40 to 100 mcg/mL. Toxic concentration: above 120 mcg/mL.

**Reference Values:**
- Therapeutic: 40-100 mcg/mL
- Critical value: >150 mcg/mL

**Clinical References:**

### Ethotoin (Peganone)

**Reference Values:**
Reference Range: 8.0 - 20.0 ug/mL

Please note: The therapeutic range for ethotoin is not well established.

Many patients respond well to ethotoin concentrations up to 60 ug/mL.

### Ethyl Glucuronide Confirmation, Chain of Custody, Random, Urine

**Clinical Information:** Ethyl glucuronide and ethyl sulfate are minor metabolites of ethanol that are detectable in body fluids following alcohol consumption and, less commonly, following extraneous exposure. Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are direct biomarkers or metabolites of ethanol. EtG and EtS can be detected up to 5 days in urine using a cutoff of 500 ng/mL.(1) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could
be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Monitoring abstinence in clinical and justice system settings using ethyl glucuronide and ethyl sulfate as direct biomarkers or metabolites of ethanol. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** A positive interpretation will be given if either the ethyl glucuronide result is greater than or equal to 250 ng/mL and/or the ethyl sulfate is greater than or equal to 100 ng/mL. A "high" positive (ie, >1,000 ng/mL) may indicate: -Heavy drinking on the same day or previously (ie, previous day or 2). -Light drinking the same day A "low" positive (ie, 500-1,000 ng/mL) may indicate: -Previous heavy drinking (ie, previous 1-3 days). -Recent light drinking (ie, past 24 hours). -Recent intense "extraneous" exposure (ie, within 24 hours or less). A "very low" positive (ie, 100-500 ng/mL) may indicate: -Previous heavy drinking (ie, 1-3 days) -Previous light drinking (ie, 12-36 hours). -Recent "extraneous" exposure.

**Reference Values:**
Negative
Cutoff concentrations: 
Ethyl Glucuronide: 500 ng/mL

**Clinical References:**
2. The role of biomarkers in the treatment of alcohol use disorders. 2012 Revision
Substance Abuse and Mental Health Services Administration. Spring 2012;11(2):1-7

**ETGC 63421**

**Ethyl Glucuronide Confirmation, Random, Urine**

**Clinical Information:** Ethyl glucuronide and ethyl sulfate are minor metabolites of ethanol which are detectable in body fluids following alcohol consumption and less commonly following extraneous exposure.

**Useful For:** Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are direct biomarkers or metabolites of ethanol. EtG and EtS can be detected up to 5 days in urine using a cutoff of 500 ng/mL.(1) These biomarkers are often used in monitoring abstinence in clinical and justice system settings.

**Interpretation:** A positive interpretation will be given if either the ethyl glucuronide result is greater than or equal to 250 ng/mL and/or the ethyl sulfate is greater than or equal to 100 ng/mL. A "high" positive (ie, >1,000 ng/mL) may indicate: -Heavy drinking on the same day or previously (ie, previous day or 2). -Light drinking the same day A "low" positive (ie, 500-1,000 ng/mL) may indicate: -Previous heavy drinking (ie, previous 1-3 days). -Recent light drinking (ie, past 24 hours). -Recent intense "extraneous" exposure (ie, within 24 hours or less). A "very low" positive (ie, 100-500 ng/mL) may indicate: -Previous heavy drinking (ie, 1-3 days) -Previous light drinking (ie, 12-36 hours). -Recent "extraneous" exposure.(2)

**Reference Values:**
Negative

**Clinical References:**
2. The role of biomarkers in the treatment of alcohol use disorders. 2012 Revision
Substance Abuse and Mental Health Services Administration. Spring 2012;11(2):1-7

**ETGR 63419**

**Ethyl Glucuronide Screen with Reflex, Random, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is...
designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened for. Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days.

**Useful For:** Screening for drug abuse involving alcohol

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry; LC-MS/MS) must be used to obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological and psychological effects.

**Reference Values:**

- **Negative**
  - Screening cutoff concentration:
    - Ethyl Glucuronide: 500 ng/mL

**Clinical References:**


**ETGS 63420 Ethyl Glucuronide Screen, Random, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened for. Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days.

**Useful For:** Screening for drug abuse involving alcohol

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry; LC-MS/MS) must be used to obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological and psychological effects.

**Reference Values:**

- **Negative**
  - Screening cutoff concentration:
    - Ethyl Glucuronide: 500 ng/mL

**Clinical References:**


FEGUC 75521

**Ethyl Glucuronide Screen, Umbilical Cord Tissue**

**Useful For:** Perinatal Drug Testing; Drug of Abuse Monitoring; Exclusion Screen; The presence of EtG in umbilical cord tissue suggests maternal exposure to ethanol, but the route of exposure (e.g., transdermal vs. oral) cannot be determined.

**Reference Values:**
Reporting limit(s) determined each analysis.
None Detected ng/g

ETGL 8749

**Ethylene Glycol, Serum**

**Clinical Information:** Ethylene glycol is present in antifreeze products, deicing products, detergents, paints, and cosmetics. Ethylene glycol has initial central nervous system (CNS) effects resembling those of ethanol and may be ingested accidentally or for the purpose of inebriation or suicide. Ethylene glycol itself is relatively nontoxic, however, metabolism of ethylene glycol by alcohol dehydrogenase (ADH) results in the formation of a number of acid metabolites, including oxalic acid and glycolic acid. These acid metabolites are responsible for much of the toxicity of ethylene glycol. Clinically poisoning has historically been divided into three stages, although timing may vary and stages may overlap. The first stage typically begins 30 minutes to 12 hours after ingestion due to the intoxicating effects of the ethylene glycol and may range from mild CNS depression to coma. The second stage begins 12 to 24 hours after ingestion and is characterized severe metabolic acidosis, due to the accumulation of acid metabolites. The third stage occurs 24 to 72 hours after ingestion and is characterized by renal failure due to calcium oxalate crystal deposition in the proximal tubules.
Ethylene glycol toxicity can be treated with 4-methylpyrazole (4-MP; fomepizole) or ethanol by competitively inhibiting alcohol dehydrogenase and thereby preventing conversion of ethylene glycol to its toxic metabolites.

**Useful For:** Confirming and monitoring ethylene glycol toxicity

**Interpretation:** Toxic concentrations greater than or equal to 20 mg/dL

**Reference Values:**
Toxic concentration: > or =20 mg/dL

**Clinical References:**

EOXD 82767

**Ethylene Oxide, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to ethylene oxide Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;=100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**ETVBF 64338**

**ETV6 (12p13.2) Rearrangement, FISH**

**Clinical Information:** Rearrangements involving 12p13 are some of the most commonly observed chromosomal abnormalities in hematologic malignancies. The ETV6 gene (ETS variant gene 6) codes for a transcription factor and is involved in deletions and translocations in both myeloid and lymphoid malignancies. Over 30 translocation partners have been identified.

**Useful For:** Providing diagnostic and prognostic information for patients with various lymphoid and myeloid malignancies

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the ETV6 locus, which can be useful for diagnosis. A negative result suggests no rearrangement of the ETV6 gene region at 12p13.2.

**Reference Values:**

An interpretive report will be provided.


ETV6F

ETV6 (12p13.2) Rearrangement, FISH, Tissue

Clinical Information: ETV6 rearrangement is a recurrent abnormality in mammary analogue secretory carcinoma, secretory carcinoma of the breast, and infantile fibrosarcoma, but is not observed in tumors that share clinical and pathologic similarities.

Useful For: Providing diagnostic information and guiding treatment primarily for patients with mammary analogue secretory carcinoma, secretory carcinoma of the breast, and infantile fibrosarcoma

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the ETV6 locus, which can be useful for diagnosis. A negative result suggests no rearrangement of the ETV6 gene region at 12p13.2.

Reference Values:
An interpretive report will be provided.


EUCL

Eucalyptus, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to eucalyptus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
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<tbody>
<tr>
<td>0</td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FECLT** 57810

**Euglobulin Clot Lysis Time**

**Reference Values:**

>60 min

**EMAY** 82846

**Euroglyphus maynei, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Euroglyphus maynei Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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

Useful For: Establishing a diagnosis of an allergy to European hornet Defining the allergen responsible for eliciting signs and symptoms Identifying allergens - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


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**Everolimus, Blood**

**Clinical Information:** Everolimus is an immunosuppressive agent derived from sirolimus (rapamycin). Both drugs function via inhibition of mTOR signaling and share similar pharmacokinetic and toxicity profiles. Everolimus has a shorter half-life than sirolimus, which allows for more rapid achievement of steady-state pharmacokinetics. Everolimus is extensively metabolized, primarily by cytochrome P450 (CYP) 3A4, thus its use with inducers or inhibitors of that enzyme may require dose adjustment. The most common adverse effects include hyperlipidemia, thrombocytopenia, and nephrotoxicity. Everolimus is useful as adjuvant therapy in renal cell carcinoma and other cancers. It recently gained FDA approval for prophylaxis of graft rejection in solid organ transplant, an application which has been accepted for years in Europe. The utility of therapeutic drug monitoring has not been established for everolimus as an oncology chemotherapy agent; however, measuring blood drug concentrations is common practice for its use in transplant. Therapeutic targets vary depending on the transplant site and institution protocol. Guidelines for heart and kidney transplants suggest that trough (immediately prior to the next scheduled dose) blood concentrations between 3 and 8 ng/mL provide optimal outcomes.

**Useful For:** Management of everolimus immunosuppression in solid organ transplant

**Interpretation:** Therapeutic targets vary by transplant site and institution protocol. Heart and kidney transplant guidelines suggest a therapeutic range of 3 to 8 ng/mL. Measurement of drug concentrations in oncology chemotherapy is less common, thus no therapeutic range is established for this application.

**Reference Values:**

3-8 ng/mL

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

**Clinical References:**


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**Ewing Sarcoma (EWS), 22q12 (EWSR1) Rearrangement, FISH, Tissue**

**Clinical Information:** Ewing sarcoma (EWS)/primitive neuroectodermal tumors (PNET) are members of the small, round cell group of tumors that are thought to originate in cells of primitive neuroectodermal origin with variable degrees of differentiation. The small, round cell group of tumors also includes rhabdomyosarcomas, desmoplastic small, round cell tumors, and poorly differentiated synovial sarcomas. Although immunohistochemical markers can be helpful in the correct diagnosis of these tumors, recent molecular studies have shown the specificity of molecular markers in differentiating
specific subtypes of small, round blue-cell tumors. Accurate diagnosis of each tumor type is important for appropriate clinical management of patients. Ewing tumors are characterized cytogenetically by rearrangements of the EWSR1 gene at 22q12 with FLI1 at 11q24 (t[11;22]) or ERG at 21q22 (t[21;22]) in 85% and 5% to 10% of Ewing tumors, respectively. Less than 1% of cases may have other fusion partners such as ETV1 at 7p22, E1AF at 17q12, or FEV at 2q33. Detection of these transcripts by reverse transcriptase-PCR (RT-PCR) (EWS, Ewing Sarcoma RT-PCR) that allows specific identification of the t(11;22) and the t(21;22), has greatly facilitated the diagnosis of Ewing tumors. However, if the quality of the available RNA is poor, the results are equivocal, or if a rare translocation partner is present, FISH testing has proven to be useful in identifying the 22q12 EWS gene rearrangement in these tumors.

**Useful For:** Supporting the diagnosis of Ewing sarcoma (EWS)/primitive neuroectodermal tumor (PNET), myxoid chondrosarcoma, desmoplastic small, round cell tumor, clear cell sarcoma, and myxoid liposarcoma when used in conjunction with an anatomic pathology consultation An aid in the diagnosis of EWS when reverse transcriptase-PCR results are equivocal or do not support the clinical picture

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the EWSR1 FISH probe set. A positive result is consistent with a diagnosis of Ewing sarcoma (EWS)/primitive neuroectodermal tumors (PNET). A negative result suggests that a EWSR1 rearrangement is not present but does not exclude the diagnosis of EWS/PNET.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. World Health Organization Classification of Tumors. Pathology and Genetics Tumours of Soft Tissue and Bone. Edited by CDM Fletcher, KK Unni, F Mertens: IARC Press; Lyon 2002, pp 298-300

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**FEBGP 75552**

**Exotic Bird Panel IgG**

**Clinical Information:** Although there have been many publications concerning the measurement of allergen-specific IgG, the clinical utility of such tests has not been established except in special situations. Thus, the quantitative IgG test should only be ordered by specialists who recognize the limitations of the test. The normal reference ranges reported represent the expected results for individuals who have no unusual exposure and have not been immunized with the indicated allergen. The ranges reported have no disease-associated significance.

**Reference Values:**
- Canary Feathers IgG
- Finch Feathers IgG
- Parrot Australian (Budgerigar) Droppings IgG
- Pigeon Feathers IgG

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**FACT 61620**

**F-Actin Ab, IgG, Serum**

**Clinical Information:** Autoimmune hepatitis (AIH) is caused by chronic inflammation within the liver, resulting in damage to the hepatocytes.(1) Initially, patients with AIH may be clinically asymptomatic, usually identified only through an incidental finding of abnormal liver function tests. At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, or ascites,
which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies. There are several autoantibodies associated with AIH, although the most common is anti-smooth muscle antibody (anti-SMA).(2) SMAs are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of anti-SMAs in the context of AIH has been identified as filamentous-actin (F-actin).(2) Because the clinical symptoms of AIH are nonspecific, being found in a variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published, and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(3) The combination of autoantibody serology, specifically anti-SMAs and anti-F-actin antibodies with liver histology, and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis.

**Useful For:** Evaluating patients with chronic liver disease in whom the diagnosis of chronic active autoimmune hepatitis is suspected

**Interpretation:** Seropositivity for anti-filamentous-actin (F-actin) antibodies is consistent with a diagnosis of autoimmune hepatitis (AIH). A negative result for anti-F-actin antibodies does not exclude a diagnosis of AIH. In a study conducted at Mayo Clinic, the F-actin enzyme-linked immunosorbent assay (ELISA) had a clinical sensitivity of 92.9% when using the manufacturer's recommended cutoff of 20.0 U. In addition, the F-actin ELISA had a clinical specificity of 76.7% when using the aforementioned cutoffs. See Supportive Data.

**Reference Values:**
- Negative: <20.0 U
- Weak Positive: 20.0-30.0 U
- Positive: >30.0 U

**Clinical References:**

**F12NG**

**F12 Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Factor XII (FXII) is a serine protease capable of activating factor VII and factor IX to their active forms but does not appear to significantly contribute to hemostasis. Rather, factor XII activity appears directed more toward inflammatory response through activation of the kallikrein-kinin system (KKS). Pathogenic alterations in the F12 gene, which encodes FXII, can cause one of two different phenotypes. Alterations in F12 that reduce the amount of plasma FXII or disrupt its functional activity result in FXII deficiency. Alterations in F12 that disrupt glycosylation or lead to increased contact-mediated autoactivation of zymogen FXII are associated with hereditary angioedema (HAE) type III with normal C1 inhibitor (C1INH). A deficiency of FXII does not cause excessive bleeding tendency or abnormal bleeding even during trauma or surgery despite prolonged partial thromboplastin time (aPTT). Some with severe deficiency experience thrombosis, but a causal connection remains unknown. Individuals with FXII deficiency are generally entirely asymptomatic, making disease state classifications unnecessary. FXII deficiency is inherited in an autosomal recessive manner. Genetic testing for FXII deficiency is generally unnecessary but may be considered if prolonged activated partial thromboplastin time (aPTT) and reduced FXII activity is documented and acquired causes of low FXII are excluded. Causes of acquired (non-genetic) FXII deficiency that should be excluded prior to genetic testing include liver disease, nephrotic syndrome, and chronic granulocytic leukemia. A study of 300 healthy blood donors found that 2.3% had FXII deficiency.(2) Actual prevalence of the condition is unknown. Of note, normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15%-20%) that may not reach adult levels for greater than or equal to 180 days after birth.
Defects in F12 that increase contact-mediated FXII autoactivation and lead to excess generation of proinflammatory peptide hormone bradykinin cause hereditary angioedema (HAE) type III with normal C1 inhibitor (C1INH). HAE type III is characterized by recurrent skin swelling, abdominal pain attacks, and upper airway obstruction. Symptoms occur almost exclusively in women because estrogen exposure appears to exacerbate the condition and attacks are precipitated or worsened by high estrogen levels. However, not all females who carry FXII alterations are symptomatic, thus HAE type III is considered an autosomal dominant disorder with incomplete penetrance. Alterations in F12 are found in 20 to 30% of patient with HAE type III. Genetic testing for HAE type III may be indicated when there is a documented family history of angioedema that does not respond to chronic, high-dose antihistamine therapy, normal complement studies, normal C1INH level and function, and no exposure to medications that could cause angioedema, angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs. Of note, acquired causes of angioedema, such as B cell lymphoproliferative, the presence of autoantibodies to C1 inhibitors, and the use of renin-angiotensin-aldosterone (RAAS) blockers, should be considered and excluded prior to genetic testing of F12 for HAE type III.

**Useful For:** Genetic confirmation of hereditary angioedema (HAE) type III with the identification of an alteration in the F12 gene known or suspected to cause the condition Testing for close family members of an individual with an HAE type III diagnosis Genetic confirmation of factor XII deficiency with the identification of an alteration in the F12 known or suspected to cause the condition This test is not intended for prenatal diagnosis

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

F13NG  
**F13A1 and F13B Genes, Next-Generation Sequencing, Varies**

**Clinical Information:** Factor FXIII deficiency (FXIIIID) is a bleeding diathesis of variable severity. The prevalence of factor FXIII deficiency is currently estimated to be 1 in 2 million but the exact prevalence is unknown. The disorder is inherited in an autosomal recessive manner. Factor XIII is a transglutaminase cross-linking enzyme critical to fibrin clot stabilization. It serves to crosslink alpha and gamma fibrin chains, leading to greater clot strength and resistance to fibrinolysis. Deficiency in FXIII leads to defective crosslinking of fibrin and the formation of a weak, unstable clot. Clots may form properly but break down 24 to 48 hours later, leading to abnormal bleeding. Factor XIII is formed from two subunits: catalytic protein FXIII-A, encoded by the F13A1 gene and synthesized by megakaryocytes and certain white blood cells in bone marrow; and stabilizing protein FXIII-B, encoded by the F13B gene and synthesized in the liver. Together, two FXIII-A subunits and two FXIII-B subunits circulate in plasma as heterotetramer. Patients with FXIII caused by alteration in F13A1 (i.e., FXIII-A deficiency) typically have a severe bleeding tendency. Onset of life-threatening symptoms is early and may present as umbilical cord and central nervous system (CNS) bleeding. 80% to 90% of
patients have umbilical bleeding in neonatal period. 40% to 60% of patients have spontaneous intracranial haemorrhage within first two decades of life, making early diagnosis critical. In women, miscarriage, menorrhagia, and intraperitoneal bleeding are common without prophylaxis. Delayed wound healing is sometimes seen. Subjects with heterozygous alterations may be at risk for bleeding complications following surgery, dental extraction, or trauma. Patients with FXIII caused by alterations in F13B (FXIII-B deficiency) typically have a relatively milder bleeding tendency relative to individuals with FXIII-A deficiency. The unpredictable nature of symptoms in FXIII deficiency, its apparent rarity, and limitations in the development of laboratory tests for its detection, especially when activity levels are very low, have made genotype-phenotype correlation difficult (2). Additionally, any correlation may be impractical given the high risk of intracranial bleeding among all affected patients and the recommendation of a general prophylactic strategy at the time of diagnosis (2). However, in general, individuals with virtually undetectable functional activity typically have a severe bleeding tendency. FXIII levels between 1 and 4 IU/dL produce moderate to severe bleeding episodes. It is difficult to predict bleeding pattern in patients with alterations that cause activity level to be greater than 5% (3). Heterozygotes (i.e., individuals with only one pathogenic alteration in either F13A1 or F13B) have 50% to 70% factor activity and are typically asymptomatic, although serious bleeding episodes have been reported (4). Causes of acquired (non-genetic) factor XIII deficiency that should be excluded prior to genetic testing include several medical conditions, such as major surgery, leukemia, liver disease, Henoch-Schönlein purpura (HSP), pulmonary embolism, stroke, inflammatory bowel diseases, sepsis, and disseminated intravascular coagulation. In these acquired FXIII-deficient states, FXIIIA levels drop into the 30% to 70% range. Valproate induces a decrease in FXIII level. FXIII antibodies may develop spontaneously in patients long treated with drugs such as isoniazid, penicillin, phenytoin, practolol, and amiodarone. Development of antibodies are also reported in some cases of severe FXIII deficiency, monoclonal gammopathy of undetermined significance, rheumatoid arthritis, and systemic lupus erythematosus. Factor XIII may also develop spontaneously in elderly patients.

**Useful For:** Detecting the pathogenic alterations within the F13A1 and F13B genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XIII deficiency Genetic confirmation of hereditary factor XIII deficiency with the identification of an alteration in either the F13A1 or F13B gene known or suspected to cause the condition Testing for close family members of an individual with a factor XIII deficiency diagnosis This test is not useful for prenatal diagnosis

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**
post-operative bleeding have been described in carriers. Factor II is also known as prothrombin and is
produced by the F2 gene. Prothrombin is proteolytically cleaved to form thrombin during the coagulation
cascade. Thrombin has multiple roles in the hemostatic response to injury. These roles include the
stimulation of platelets to form a platelet plug, the cleavage of fibrinogen to form fibrin clot, the
activation of factors V and VIII by the excision of their central domains, and the activation of protein C
and protein S to start the inhibition of the coagulation process. A significant deficiency (less than 1% to
5%) in the amount of functional prothrombin can cause abnormal spontaneous or post traumatic bleeding.
It has been estimated that the minimum level of functional prothrombin needed to prevent these
symptoms is 10% to 20% of normal.(1) Alterations in the F2 gene that interfere with the production or
function of prothrombin disrupt the coagulation cascade and can lead to bleeding complications. FII
deficiency is classified into 2 types. Mutations in the F2 gene that interfere with the production of
prothrombin lead to lower levels of the protein in blood causing type I F2D, or hypoprothrombinemia.
Type I F2D may be classified as mild, moderate or severe based on the factor level in plasma. A factor
level of less than 5% is considered a severe deficiency and is characterized by severe bleeding symptoms
with bleeding typically occurring spontaneously. Moderate deficiency is defined as 5% to 10% activity
and mild deficiency is greater than 10%. Individuals who are heterozygous for a pathogenic F2 alteration
typically have factor levels of 30% to 60%. Mutations in F2 that create a dysfunctional protein that is
produced in normal amounts but isn’t active cause type II F2D, or dysprothrombinemia.
Individuals with type II F2D alterations have bleeding of variable severity that is typically less severe
than in type I F2D. Cases of compound heterozygosity for both a hypoprothrombinemia mutation and a
dysprothrombinemia mutation in the same person have been reported. Additionally, a complete absence
of prothrombin is thought to be incompatible with life. Genetic testing is indicated if a coagulation screen
shows prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), normal
thrombin time (TT), and reduced levels of prothrombin (factor II) activity. Prothrombin antigen testing
helps to distinguish between type I and type II deficiencies. Causes of acquired (non-genetic) factor II
deficiency that should be excluded prior to genetic testing include long-term use of antibiotics, impaired
vitamin K absorption, liver disease, the obstruction of bile, and warfarin anticoagulation. Cases of an
acquired factor II inhibitor can occur in the presence of a lupus anticoagulant, autoimmune disorders or
during infection or lymphoma.(2) A small number of cases are suspected to have been drug induced
(quinidine in one case and phenytoin in another).

Useful For: Ascertaining a causative alteration in F2 and the affected region of prothrombin protein
in an individual clinically diagnosed with factor II deficiency Carrier testing for close family members
of an individual with a factor II deficiency diagnosis This test is not intended for prenatal diagnosis.

Interpretation: An interpretive report will be provided. Evaluation and categorization of variants is
performed using the most recent published American College of Medical Genetics and Genomics
(ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or
possible pathogenicity and reported with interpretive comments detailing their potential or known
significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular
Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This
may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Palla R, Peyvandi F, Shapiro AD: Rare bleeding disorders: diagnosis and
anti-coagulant-hypoprothrombinemia syndrome: report of two cases and review of the literature. Lupus
2015;94(4):713-715 3. Lancellotti S, Basso M, De Cristofaro R: Congenital Prothrombin Deficiency:
2005;106(8):2605-2612

F2ISO
607698
F2-Isoprostanones, Random, Urine
Clinical Information: Oxidative stress results from an imbalance of reactive oxygen species
resulting in peroxidation of biomolecules. 15-F2t-isoprostane (F2ISO, also referred to as 8-iso-PGF2alpha or 8-isoprostane) is an F2-isoprostane and its measurement is considered the "gold standard" test for quantifying lipid peroxidation in vivo. F2ISO is a potent vasoconstrictor, induces vascular smooth muscle cell proliferation, and increased aspirin resistance to platelet aggregation. Elevated urinary F2ISO concentrations are associated with the presence and extent of coronary artery stenosis, peripheral artery disease, and increased risk of post-operative atrial fibrillation. Urinary F2ISO concentrations are lowered by aerobic exercise training, smoking cessation, and fenofibrate therapy.

**Useful For:** Assessment of in vivo lipid peroxidation Considered to be an index of systemic oxidative stress over time

**Interpretation:** Elevated urinary F2-isoprostanes reflect widespread oxidative stress and systemic burden of lipid peroxidation end products. Quantitation of F2-isoprostanes in urine is highly dependent upon the methodology utilized; however, mass spectrometry methods (gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry) assays yield superior sensitivity and analytical specificity compared with immunoassays. F2-isoprostanes demonstrate superior clinical sensitivity compared to other oxidative stress biomarkers but lack clinical specificity for any particular disease. Pharmacological treatment with antioxidant supplementation, hypoglycemic agents in diabetes, smoking cessation, and weight reduction have all been shown to decrease production of F2-isoprostanes.

**Reference Values:**
> or ≥18 years: < or =1.0 ng/mg creatinine
Reference values have not been established for patients who are <18 years of age

**Clinical References:**

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**F5 Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Factor V is a critical cofactor of Xa in the conversion of prothrombin to thrombin. Factor V protein has both procoagulant and anticoagulant properties, and molecular defects in it may result in either bleeding or clotting. Factor V deficiency (F5D, also known as parahemophilia) causes mild to severe bleeding problems, including nosebleeds, bruising, soft tissue and joint bleeds, menorrhagia, umbilical stump bleeding and post-operative bleeding. Intracranial bleeding has been reported in neonates, but bleeding episodes in the central nervous system and in the GI tract, in general, are reported to occur only rarely. F5D is a rare with a prevalence of 1 per 1 million in the general population. The F5 gene encodes Factor V. Alterations in the F5 gene that reduce the amount of plasma factor V or disrupt its functional procoagulant activity cause F5D. Unlike some other factor deficiencies, there is no strict correlation between FV levels and disease state severity, as some patients with severe deficiency do not have severe bleeding despite low FV levels. However, it has been estimated that the minimum level of factor V needed to prevent symptoms is at least 10% of normal. Hereditary factor V deficiency is considered to be an autosomal recessive disorder. Individuals homozygous or compound heterozygous for pathogenic F5D alterations usually have factor V plasma activity levels lower than 10%.(1) Heterozygous individuals typically have around 50% plasma factor V levels and are usually
asymptomatic. (1) Causes of acquired (non-genetic) F5D that should be excluded prior to genetic testing include the development of inhibitors directed against factor V after exposure to bovine thrombin or in association with risk factors like surgical procedures, antibiotic administration, blood transfusions, cancers, and autoimmune disorders. (1) In addition, liver disease or consumptive coagulopathy may result in low factor V levels. Defects in factor V may be associated with an increased risk of thrombosis. Activated protein C (APC) reduces the thrombotic activity of factor V by proteolytically cleaving certain sites in the protein. Point alterations at these cleavage sites make factor V resistant to this inactivation (i.e., cause APC resistance), abnormally prolonging its procoagulant properties and increasing the risk for thrombosis. The vast majority of individuals with familial APC resistance have a specific point alteration in the F5 gene called factor V Leiden (historically known as "R506Q" or "1691G>A"). Five percent of factor V Leiden heterozygotes develop thromboembolism by 65 years of age. Other far less common factor V alterations also cause APC resistance and have different thrombotic risks. The coinheritance of both a pathogenic APC-resistant F5 gene alteration and a F5 gene alteration that causes F5D (i.e., "pseudohomozygosity") also results in an increased risk for thrombosis. The hereditary thrombophilia that results from F5 alterations causing APC-resistance is inherited in an autosomal dominant manner that is incompletely penetrant (i.e., the presence of a pathogenic variant increases the risk for but does not guarantee manifestation of disease). These risks are further influenced by additional risk factors, such as oral contraceptive use, hyperhomocysteinemia, pregnancy, blood type, and the inheritance of other molecular defects in genes associated with heritable thrombophilia (e.g., deficiencies in protein S and protein C). Still other factors can impair activity of activated protein C such as increased factor VIII, increased estrogen levels, antiphospholipid antibodies, cancer, elevated BMI, and smoking. The prevalence of alterations in F5 that cause APC resistance other than factor V Leiden is unknown. Full gene sequencing of F5 may be warranted if APC resistance assay (see APCRV / Activated Protein C Resistance V [APCRV], Plasma) suggests abnormal resistance to activated protein C and factor V Leiden genotype does not correlate with the severity of thrombophilia or clinical presentation. During testing for APC resistance, care should be taken to avoid, when possible, certain preanalytical conditions of the patient and blood specimen that may interfere with results. Examples include the presence of lupus-like anticoagulants and specific coagulation factor inhibitors, excessive exposure to estrogen, and markedly elevated levels of factor VIII.

**Useful For:** Genetic confirmation of factor V deficiency with the identification of an alteration in the F5 gene known or suspected to cause the condition Carrier testing for close family members of an individual with a factor V deficiency diagnosis This test is not intended to evaluate for the factor V Leiden mutation. This test is not intended for prenatal diagnosis.

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**
**Fabry Disease, Full Gene Analysis, Varies**

**Clinical Information:** Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced alpha-Gal A activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual alpha-Gal A activity. Males with less than 1% alpha-Gal A activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. By middle age, most patients develop renal insufficiency leading to end-stage renal disease, as well as cardiac and cerebrovascular disease. Males with greater than 1% alpha-Gal A activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not have other symptoms of classic Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency later in life. The cardiac variant is not associated with renal failure. Female carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severe. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Alterations in the GLA gene result in deficiency of alpha-Gal A. Most of the alterations identified to date are family specific. Full sequencing of the GLA gene identifies over 98% of the sequence variants in the coding region and splice junctions. In addition, this assay detects the intron 4 alteration common in the Taiwanese population. (1) The recommended first-tier test for males with suspected Fabry disease is biochemical testing that measures alpha-galactosidase enzyme activity in blood or serum: AGAW / Alpha-galactosidase, Leukocytes or AGAS / Alpha-galactosidase, Serum. Additionally, testing for the glycosphingolipid, globotriaosylsphingosine (LGb3) may aid in further clarifying disease status in both males and females with suspected Fabry disease (LGB3 / Globotriaosylsphingosine, Serum). Individuals with decreased or absent enzyme activity and elevated LGb3 are more likely to have an identifiable alterations in the GLA gene by molecular genetic testing. However, enzymatic testing alone is not reliable to detect female carriers. The following algorithms are available in Special Instructions: -Fabry Disease: Newborn Screen-Positive Follow-up algorithm -Fabry Disease Diagnostic Testing Algorithm

**Useful For:** Confirmation of a diagnosis of classic or variant Fabry disease in affected males with reduced alpha-galactosidase A enzyme activity Carrier or diagnostic testing for asymptomatic or symptomatic females, respectively

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. (2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**Factor 13a Immunostain, Technical Component Only**

**Clinical Information:** Factor XIIIa, a blood and intracellularly produced coagulation factor, has been found in a variety of cell types, including fibroblast-like mesenchymal cells, and has been shown to...
stimulate the proliferation of fibroblasts and neoplastic cells in vitro. Immunohistochemical staining for factor XIIIa labels normal dermal dendrocytes, the large stellate fibroblasts found in acquired digital fibrokeratomas, angiofibromas, and oral fibroma, and a proportion of cells in histiocytomas. Factor XIIIa immunostain also produces cytoplasmic staining of dermal dendrocytes in normal skin and of a proportion of cells in histiocytomas.

**Useful For:** Aiding in the identification of acquired digital fibrokeratomas, angiofibromas, and oral fibroma, and a proportion of cells in histiocytomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Factor 8 Related Antigen Immunostain, Technical Component Only**

**Clinical Information:** Factor 8-related antigen shows diffuse cytoplasmic staining of endothelial cells, megakaryocytes, and platelets. This immunostain may be used to support endothelial cell lineage in angiosarcoma.

**Useful For:** Marker of endothelial cell lineage

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Factor II Inhibitor Evaluation, Plasma**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can either occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in geriatric patients.
Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to factor II This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

**Interpretation:** Normally, there is no inhibitor, ie, negative result. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR II ACTIVITY ASSAY**

- Adults: 75-145%
- Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Clinical References:**


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2AINH 607445

**Factor II Inhibitor Profile, Professional Interpretation**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can either occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in geriatric patients. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Interpretation of testing for the detection and quantitation of inhibitor to factor II

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**

Only orderable as a reflex. For more information see 2INHE / Factor II Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**


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2INHT 607438

**Factor II Inhibitor Profile, Technical Interpretation**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can either occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in geriatric patients. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to factor II This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.
**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as part of a profile. For more information see 2INHE / Factor II Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

**Factor II Inhibitor Screen, Plasma**

**Clinical Information:**
Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

**Useful For:** Detecting the presence of a specific factor inhibitor directed against coagulation factor II

**Interpretation:** An interpretive report will be provided when testing is completed.

**Reference Values:**
Only orderable as part of a profile. For more information see:
- 2INHE / Factor II Inhibitor Evaluation, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- APROL / Prolonged Clot Time Profile, Plasma

**Clinical References:**

**Factor IX Inhibitor Evaluation, Plasma**

**Clinical Information:**
Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

**Useful For:** Detection and titering of coagulation inhibitor to the specific factor requested, primarily factor IX in patients with hemophilia B. This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

**Interpretation:** Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.
Reference Values:
FACTOR IX ACTIVITY ASSAY
Adults: 65-140%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%), which may not reach adult levels for > or =180 days postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.


Factor IX Inhibitor Profile Technical Interpretation

Clinical Information: Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

Useful For: Technical interpretation of coagulation inhibitor testing to the specific factor requested, primarily factor IX in patients with hemophilia B

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as part of a profile. For more information see 9INHE / Factor IX Inhibitor Evaluation, Plasma.

An interpretive report will be provided.


Factor IX Inhibitor Profile, Professional Interpretation

Clinical Information: Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

Useful For: Interpretation for the detection and titering of coagulation inhibitor to the specific factor requested, primarily factor IX in patients with hemophilia B

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as a reflex. For more information see 9INHE / Factor IX Inhibitor Evaluation, Plasma

An interpretive report will be provided.

**Factor IX Inhibitor Screen, Plasma**

**Clinical Information:** Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

**Useful For:** Detecting the presence of a specific factor inhibitor directed against coagulation factor IX

**Interpretation:** An interpretive report will be provided when testing is completed.

**Reference Values:**
Only orderable as a reflex. For more information see:
- 9INHE / Factor IX Inhibitor Evaluation, Plasma
- ALUPP / Lupus Anticoagulant Profile, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- APROL / Prolonged Clot Time Profile, Plasma

**Clinical References:**

**Factor IX Known Mutation Sequencing**

**Reference Values:**
Only orderable as a reflex at order entry for unit code FIXKM / Hemophilia B, Factor IX Gene Known Mutation Screening (Carrier Detection).

**Factor V Bethesda Units, Plasma**

**Clinical Information:** Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

**Useful For:** Detecting and quantifying the presence and titer of a specific factor inhibitor directed against a specific coagulation factor

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma
5INHE / Factor V Inhibitor Evaluation, Plasma

< or = 0.5 Bethesda Units


Factor V Inhibitor Evaluation, Plasma

Clinical Information: Factor V inhibitors can occur in patients with congenital factor V deficiency after transfusion of fresh frozen plasma, however, they more commonly occur spontaneously in previously healthy older patients who have no underlying diseases. Topical bovine thrombin or fibrin glue, which contain bovine thrombin and factor V, are commonly used in surgery for topical hemostasis and can result in development of anti-bovine thrombin/factor V inhibitors that cross-react with human thrombin and factor V. Other associations include antibiotics, transfusions, and malignancies.

Useful For: Detection and quantitation of inhibitors against coagulation factor V. This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor, ie, negative result. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR V ACTIVITY ASSAY
Adults: 70-165%
Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =30-35%) which reach adult levels within 21 days postnatal.*
Healthy premature infants (30-36 weeks gestation) may have borderline low or mildly decreased levels.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.


Factor V Inhibitor Profile, Professional Interpretation

Clinical Information: Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

Useful For: Interpretation of testing for factor V inhibitors

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as a reflex. For more information see 5INHE / Factor V Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

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### Factor V Inhibitor Profile, Technical Interpretation

**Clinical Information:** Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

**Useful For:** Interpretation of the detecting and quantifying the presence and titer of a specific factor inhibitor directed against a specific coagulation factor

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as part of a profile. For more information see 5INHE / Factor V Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

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### Factor V Inhibitor Screen, Plasma

**Clinical Information:** Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Nonspecific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

**Useful For:** Detecting the presence of a specific factor inhibitor directed against coagulation factor V

**Interpretation:** An interpretive report will be provided when testing is completed.

**Reference Values:**
Only orderable as part of a profile. For more information see:
5INHE / Factor V Inhibitor Evaluation, Plasma
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma

Negative


**FFVLM 75529**

**Factor V Leiden (F5) R506Q Mutation**

**Clinical Information:** Venous thromboembolism (VTE) is a multifactorial condition caused by a combination of genetic and environmental factors. The Factor V Leiden (FVL) variant is the most common cause of inherited VTEs, accounting for over 90 percent of activated protein C (APC) resistance. Because the FVL variant eliminates the APC cleavage site, factor V is inactivated slower, thus persisting longer in blood circulation, leading to more thrombin production. Other genetic risk factors for VTE include, male sex and variants in antithrombin, protein C, protein S, or factor XIII. Non-genetic risk factors include, age, smoking, prolonged immobilization, malignant neoplasms, surgery, pregnancy, oral contraceptives, estrogen replacement therapy, tamoxifen and raloxifene therapy. Note: This test is not recommended for nonsymptomatic patients under 18 years of age.

**Reference Values:**
Negative: This sample is negative for factor V Leiden, R506Q mutation.

**F7NGS 65165**

**Factor VII Deficiency, F7 Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Factor VII (FVII) deficiency (F7D) is a bleeding diathesis. Most patients with mild FVII deficiency do not experience spontaneous bleeding but may experience prolonged bleeding after trauma or surgical interventions. For patients with severe factor VII deficiency, symptoms include epistaxis, menorrhagia, easy bruising, gum bleeding, and post-surgical bleeding. Joint and muscle bleeds are less common. In severe deficiencies, bleeding starts within the first 6 months of life and can include life-threatening intracranial and gastrointestinal hemorrhages. (1) Additionally, FVII deficiency does not protect patients from venous thromboembolism. Between 3% and 4% of F7D patients experience thrombotic events, particularly deep vein thrombosis. These events are associated with surgery and factor replacement therapy, but spontaneous thrombosis may also occur. (2) The severity of these symptoms is highly variable, ranging from mild to lethal. (3) Hereditary factor VII deficiency has an estimated prevalence of 1 in 500,000. If genetic, F7D is inherited in an autosomal recessive manner with variable expressivity. Both males and females may be affected. Hereditary F7D results from defects in the concentration or function of coagulation factor VII, a critical activator of the coagulation cascade. When an injury to a blood vessel releases tissue factor into the blood stream, coagulation factor VII binds with tissue factor to initiate the blood coagulation cascade. However, disease severity correlates poorly with FVII activity levels in blood plasma. FVII levels of less than 2% typically result in severe hemorrhagic disease, but not always. Conversely, plasma factor VII levels greater than 20% do not typically cause symptoms, yet some patients with levels ranging from 20% to 50% have abnormal bleeding. (4) The F7 gene encodes factor VII. Alterations in the F7 gene that reduce the amount of FVII can lead to an impaired response to vascular injuries and abnormal bleeding. Genetic testing may be indicated if a coagulation screen shows increased prothrombin time (PT), and factor VII activity that is less than 65% (note: Reference range may vary depending on the locally established reference range). Of note, normal full-term newborn infants or healthy premature infants have factor VII levels equal to or greater than 20%, which increases within the first postnatal week but may not reach adult levels for 180 days or more. Causes of acquired (non-genetic) factor VII deficiency that should be excluded prior to genetic testing include Vitamin K deficiency, use of vitamin K antagonists like warfarin, liver disease, sepsis, can cause...
acquired factor VII deficiency (6, 7). Warfarin or similar anticoagulants also decrease factor VII synthesis. These acquired causes of FVII deficiency should be considered prior to genetic testing.

**Useful For:** Genetic confirmation of a factor VII deficiency diagnosis with the identification of a known or suspected pathogenic alteration in the F7 gene Carrier testing for close family members of an individual with a factor VII deficiency diagnosis This test is not useful for prenatal diagnosis.

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**

An interpretive report will be provided

**Clinical References:**


**Factor VII Inhibitor Evaluation, Plasma**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor VII This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

**Interpretation:** Normally, there is no inhibitor, ie, negative result. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR VII ACTIVITY ASSAY**

Adults: 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%), which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Clinical References:**

Factor VII Inhibitor Profile, Professional Interpretation

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Interpretation of testing for the detection and quantitation of inhibitor to factor VII

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as a reflex. For more information see 7INHE / Factor VII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

Factor VII Inhibitor Profile, Technical Interpretation

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Technical interpretation of inhibitor to coagulation factor VII testing

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as part of a profile. For more information see 7INHE / Factor VII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

Factor VII Inhibitor Screen, Plasma

**Clinical Information:** Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from
transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor VII

Interpretation: An interpretive report will be provided when testing is completed.

Reference Values:
Only orderable as part of a profile. For more information see:
7INHE / Factor VII Inhibitor Evaluation, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma

Negative


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8INHE
607424

**Factor VIII Inhibitor Evaluation, Plasma**

**Clinical Information:** Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Elderly non-hemophilic patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

Useful For: Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR VIII ACTIVITY ASSAY
Adults: 55-200%

Normal, full-term newborn infants or healthy premature infants typically have levels greater or equal to 40%.*

*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.


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8AINH
607442

**Factor VIII Inhibitor Profile, Professional Interpretation**

**Clinical Information:** Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Elderly non-hemophilic patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

Useful For: Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR VIII ACTIVITY ASSAY
Adults: 55-200%

Normal, full-term newborn infants or healthy premature infants typically have levels greater or equal to 40%.*

*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

non-hemophiliac patients (not previously factor VIII deficient) - Women in postpartum period - Patients with other autoimmune illnesses

**Useful For:** Interpretation for the detection of the presence and titer of a specific factor inhibitor directed against coagulation factor VIII

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as a reflex. For more information see 8INHE / Factor VIII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

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**Factor VIII Inhibitor Profile, Technical Interpretation**

**Clinical Information:** Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: - Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate - Elderly nonhemophiliac patients (not previously factor VIII deficient) - Women in postpartum period - Patients with other autoimmune illnesses

**Useful For:** Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII. This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as part of a profile. For more information see 8INHE / Factor VIII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

**Clinical References:**

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**Factor X Deficiency, F10 Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Factor X (FX) deficiency (F10D) is a bleeding diathesis of variable severity that may appear at any age, although more severely affected patients, who typically have FX activity less than 1%, present early in life. Symptoms include umbilical stump bleeding, intracranial hemorrhage, gastrointestinal bleeding, joint bleeds, and hematomas. The most severe clinical symptoms are uncommon in a patient with FX activity levels greater than 2%. Regardless of disease severity, the most common bleeding symptom is nose bleeds. Menorrhagia occurs in more than half of women with F10D but miscarriages are not common. Antepartum and postpartum hemorrhage are reportedly common in women with F10D and also has been reported in heterozygous females. F10D is estimated to affect 1 in 1,000,000 people. If genetic, F10D is inherited in an autosomal recessive manner. Both males and females may be
affected. Hereditary F10D results from defects in the concentration or function of coagulation FX, a vitamin-K dependent protein synthesized in the liver that is essential for stopping blood loss after injury. FX circulates in blood plasma as an inactive zymogen. It is activated by either the intrinsic or extrinsic pathway and is the most important activator of prothrombin, which has multiple roles in the hemostatic response to injury. The F10 gene produces coagulation FX. Alterations in the F10 gene can interfere with the production of coagulation FX, leading to lower levels of the factor in blood (type I F10D) or dysfunctional factor protein that is produced in normal amounts (type II F10D). The bleeding tendency in F10D is variable and does not always correlate with circulating FX antigen levels. In general, however, lower FX activity levels predict a higher risk for bleeding. FX activity of less than 1% of normal is associated with severe F10D, activity of 1% to 5% of normal is associated with moderate disease, and a FX activity of 6% to 10% is associated with mild disease. Of note, normal, full-term newborn infants or healthy premature infants may have decreased levels (greater than or equal to 15% to 20% of normal), which may not reach adult levels for greater than or equal to 180 days after birth. Acquired deficiency of FX is more common than hereditary F10D. Causes of acquired (non-genetic) F10D that should be excluded prior to genetic testing include liver disease, warfarin therapy, vitamin K deficiency, and (rarely) inhibitors. Acquired isolated F10D is seen in 6% to 14% of individuals with primary amyloidosis. Other conditions associated with acquired isolated F10D include underlying malignancy, especially acute myeloid leukemia, and respiratory infection. Conditions associated with acquired F10D should be considered prior to genetic testing.

**Useful For:** Genetic confirmation of a factor X deficiency diagnosis with the identification of a known or suspected pathogenic alterations in the F10 gene. Carrier testing for close family members of an individual with a factor X deficiency diagnosis. This test is not intended for prenatal diagnosis.

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**10INE 607429**

**Factor X Inhibitor Evaluation, Plasma**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or they can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and advanced age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor X. This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant,
or other inhibitors that are not specific for coagulation factors.

**Interpretation:** Normally, there is no inhibitor, ie, negative result. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

<table>
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<th>Value</th>
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</thead>
<tbody>
<tr>
<td><strong>FACTOR X ACTIVITY ASSAY</strong></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>70-150%</td>
</tr>
</tbody>
</table>

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Factor X Inhibitor Screen, Plasma**

**Clinical Information:** Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

**Useful For:** Detecting the presence of a specific factor inhibitor directed against coagulation factor X

**Interpretation:** An interpretive report will be provided when testing is completed.

**Reference Values:**
Only orderable as a reflex. For more information see:
- 10INE / Factor X Inhibitor Evaluation, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- APROL / Prolonged Clot Time Profile, Plasma

Negative


**Factor XI Inhibitor Evaluation, Plasma**

**Clinical Information:** Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C) or after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor XI This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

**Interpretation:** Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**
- FACTOR XI ACTIVITY ASSAY
  - Adults: 55-150%
  - Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) which may not reach adult levels for > or =180 days postnatal.*
  - *See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

**Factor XI Inhibitor Profile, Professional Interpretation**

**Clinical Information:** Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C) or after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

**Useful For:** Interpretation of the detection and quantitation of inhibitor to coagulation factor XI

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as a reflex. For more information see 11INE / Factor XI Inhibitor Evaluation, Plasma.

**Clinical References:**

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**Factor XI Inhibitor Profile, Technical Interpretation**

**Clinical Information:** Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C) or after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

**Useful For:** Interpretation of the detection and quantitation of inhibitor to coagulation factor XI. This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as part of a profile. For more information see 11INE / Factor XI Inhibitor Evaluation, Plasma.

**Clinical References:**

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**Factor XI Inhibitor Screen, Plasma**

**Clinical Information:** Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (e.g., prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

**Useful For:** Detecting the presence of a specific factor inhibitor directed against coagulation factor XI
**Interpretation:** An interpretive report will be provided when testing is completed.

**Reference Values:**
Only orderable as part of a profile. For more information see:
- 11INE / Factor XI Inhibitor Evaluation, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- APROL / Prolonged Clot Time Profile, Plasma

Negative


**Factor XIII (13), Screen, Plasma**

**Clinical Information:** Factor XIII is found in plasma and platelets. Plasma factor XIII consists of 2 A-subunits and 2 B-subunits; platelet factor XIII consists of only 2 A-subunits. After factor XIII is activated by thrombin, it catalyzes the formation of peptide bonds between adjacent molecules of fibrin monomers, thus conferring mechanical and chemical stability to the fibrin clot. Fibrin that is not covalently cross-linked exhibits an increased susceptibility to fibrinolysis. Congenital factor XIII deficiency is an autosomal recessive bleeding disorder. Homozygous individuals (FXIII <1%) experience soft tissue hemorrhage, hemarthrosis, and hematomas. Typically, affected patients suffer from delayed bleeding occurring 24 to 48 hours after the initial hemostatic response to an injury. In newborns, bleeding from the umbilical stump may occur after separation of the umbilical cord, as well as intracranial bleeding. Poor wound healing and abnormal scar formation is also observed. Heterozygous carriers may be asymptomatic; however, females may experience recurrent spontaneous abortions. Acquired factor XIII deficiency is rare and typically occurs as a result of development of autoantibodies. These patients develop adult-onset bleeding.

**Useful For:** Screening for factor XIII deficiency

**Interpretation:** Normally, no clot dissolution is observed after 30 minutes in 1% monochloroacetic acid. Clot dissolution begins once factor XIII levels are reduced to 1% or 2%.

**Reference Values:**
Only orderable as part of a profile. For more information see ALBLD / Bleeding Diathesis Profile, Limited, Plasma.

Normal


**Factor XIII, Functional**

**Clinical Information:** Factor XIII, Functional- Low Factor XIII levels, i.e., <15%, may cause a bleeding disorder and levels <2% have been associated with spontaneous intracranial hemorrhage.

**Reference Values:**
57 - 192 % activity

**Factor XIII, Qualitative, with Reflex to Factor XIII 1:1 Mix**

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
False Ragweed, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to false ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<th>Class</th>
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</tr>
<tr>
<td>1</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


FDP

Familial Dysautonomia, Mutation Analysis, IVS20(+6T->C) and R696P, Varies

**Clinical Information:** Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons. Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal degeneration continues throughout the lifespan. Mutations in the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein gene (IKBKAP) cause the clinical manifestations of familial dysautonomia. The carrier rate in the Ashkenazi Jewish population is 1 in 31. There are 2 common
mutations in the Ashkenazi Jewish population: IVS20(+6)T->C and R696P. The carrier detection rate for these 2 mutations is 99%.

**Useful For:** Carrier screening for familial dysautonomia in individuals of Ashkenazi Jewish ancestry
Prenatal diagnosis of familial dysautonomia in at-risk pregnancies Confirmation of a clinical diagnosis of familial dysautonomia in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

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**FHRGP 65748**

**Familial Hypercholesterolemia and Related Disorders Multi-Gene Panel, Next-Generation Sequencing, Varies**

**Clinical Information:** Familial hypercholesterolemia (FH) is an inherited condition that results in elevated levels of low-density lipoprotein cholesterol (LDL-C). FH is associated with premature cardiovascular disease and myocardial infarction. Early diagnosis and treatment help to mitigate these risks. The most common form of FH is autosomal dominant heterozygous familial hypercholesterolemia (heFH) caused by loss-of-function variants found in the LDLR gene. Recent studies suggest that the prevalence of heFH is as high as 1 in 200 to 250, and may be even higher in some founder populations such as those of French Canadian, Ashkenazi Jewish, Lebanese, and South African descent. In general, FH heterozygotes have 2-fold elevations in plasma cholesterol and develop coronary atherosclerosis after the age of 30. Hundreds of variants have been identified in the LDLR gene. The majority of variants in the LDLR gene are small point variants (missense, nonsense) or small insertions or deletions. Most of these variants are detectable by sequencing of the LDLR gene. An additional 10% of variants in the LDLR gene are large intragenic rearrangements, such as large exon deletions and duplications.

Absent or decreased LDL-receptor results in a reduced capacity to clear LDL from circulation. A more severe form of familial hypercholesterolemia can also be caused by homozygous or compound heterozygous (biallelic) variants in the LDLR gene. This condition is referred to as homozygous familial hypercholesterolemia (hoFH). Recent studies suggest the prevalence of hoFH is as high as 1 in 250,000. Individuals with homozygous FH typically have severe hypercholesterolemia (generally >650 mg/dL) with the presence of cutaneous xanthomas prior to 4 years of age, childhood coronary heart disease, and oftentimes, death from myocardial infarction prior to 20 years of age. Another form of autosomal dominant hypercholesterolemia is called familial defective apolipoprotein B-100 (FDB). FDB is caused by loss-of-function variants in the APOB gene that reduce the binding affinity between the protein encoded by APOB (apolipoprotein B-100) and the protein encoded by LDLR (low-density lipoprotein receptor). Individuals with heterozygous APOB variants have elevated LDL-C, although the elevation is typically less than that observed in individuals with heterozygous LDLR variants; increased rates of coronary artery calcifications; and premature myocardial infarction. Approximately 1 in 1667 Northern European Caucasians carry the R3500Q (HGVS: c.10580G>A, p.Arg3527Gln) variant in the APOB gene, and approximately 1 in 800 East Asians carry the R3500W (HGVS: c.10579C>T, p.Arg3527Trp) variant in the APOB gene. Although other variants resulting in autosomal dominant hypercholesterolemia have been described in APOB; most appear within a hotspot (or frequently affected) region surrounding the p.Arg3527 residue. Homozygosity and compound heterozygosity for APOB variants can also occur; these individuals typically have LDL-C levels above 300 mg/dL.

Individuals with homozygous FDB are sometimes misdiagnosed with heFH. Autosomal dominant hypercholesterolemia can also be caused by gain-of-function variants in the PCSK9 gene. Variants in this gene are rare, but when present, they result in increased PCSK9 protein levels, leading to increased degradation of low-density lipoprotein receptors. Recently, drugs targeting PCSK9 (called PCSK9 inhibitors) have been developed. These drugs inhibit the binding of PCSK9 to LDL-receptors, thus reducing degradation of LDL-receptors and increasing the amount of LDL-C cleared in certain
individuals. Loss-of-function variants in the LDLRAP1 gene cause a rare form of familial hypercholesterolemia called autosomal recessive familial hypercholesterolemia. Once LDL-C binds to the LDL-receptor the LDLRAP1 protein binds to the complex and internalization of the complex, which results in degradation of either the LDL particle or the entire complex occurs. Unlike autosomal dominant hypercholesterolemia caused by heterozygous variants in LDLR, APOB, and PCSK9, biallelic variants in LDLRAP1 are required for elevated LDL-C levels. Individuals with homozygous or compound heterozygous LDLRAP1 variants typically have LDL-C levels above 400 mg/dL, cutaneous and tendon xanthomas, and coronary artery disease. Heterozygosity for LDLRAP1 variants does not result in elevated cholesterol levels, so the parents of children with biallelic LDLRAP1 variants are typically normocholesterolemic. Sitosterolemia, a rare autosomal recessive inherited lipid metabolism disease, is caused by biallelic variants in the ABCG5 or ABCG8 genes and has similar clinical manifestations to familial hypercholesterolemia. Sitosterolemia is characterized by increased intestinal absorption of plant sterols (15% to 60% compared to <5% in unaffected individuals). These individuals also typically have elevated total cholesterol and LDL cholesterol levels, although individuals with normal LDL-C levels have also been reported. Untreated individuals with sitosterolemia exhibit tendon and tuberous xanthomas in childhood, premature atherosclerosis, myocardial infarction, and coronary heart disease. At least one report of an individual with sitosterolemia being misdiagnosed with homozygous FH has been reported. The authors noted that the Dutch Lipid Clinic Network diagnostic (DLCN) criteria could not distinguish between homozygous FH and sitosterolemia in this individual. Identification of the genetic cause of an individual's clinical features helps to determine the appropriate treatment for their clinical features. Treatment is aimed at lowering plasma LDL levels and plasma sterol levels. Common treatments included statins, LDL apheresis, dietary modifications, and more recently PCSK9 inhibitors. Screening of at-risk family members allows for effective primary prevention by instituting appropriate therapy and dietary modifications at an early stage. Table 1. Genes included in the Familial Hypercholesterolemia and Related Disorders Multigene Panel Gene Symbol (alias) Protein OMIM Inheritance Phenotype Disorder ABCG5 ATP-binding cassette, subfamily G, member 5 605459 AR Sitosterolemia ABCG8 ATP-binding cassette, subfamily G, member 8 605460 AR Sitosterolemia APOB Apolipoprotein B 107730 AD AR Hypercholesterolemia, due to ligand-defective apo B Hypobetalipoproteinemia LDLR Low density lipoprotein receptor 606945 AD AR Hypercholesterolemia familial LDLRAP1 Low density lipoprotein receptor adaptor protein 1 605747 AR Hypercholesterolemia, familial, autosomal recessive PCSK9 Proprotein convertase, subtilisin/kexin-type, 9 607786 AD Hypercholesterolemia, familial, 3 AD: autosomal dominant AR: autosomal recessive

**Useful For:** Confirming a clinical diagnosis of familial hypercholesterolemia or sitosterolemia Cascade screening of at-risk family members and early diagnosis, treatment, and dietary modifications

Ascertaining carrier status of family members of individuals diagnosed with familial hypercholesterolemia for genetic counseling purposes

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

Inference in Autosomal Recessive Hypercholesterolemia. Arterioscler Thromb Vasc Biol 

**FMTT**

**Familial Mutation, Targeted Testing, Varies**

**Clinical Information:** This test is available for the analysis of up to 4 genetic variants (single 
nucleotide variant, small insertion/deletion, or exon level deletion/duplication). Targeted testing is used 
for diagnostic or predictive testing in family members of an affected individual with a previously 
detected variant, carrier screening, segregation analysis, confirmation of research results, or testing for 
germline status of a variant detected by somatic or tumor testing. This test is available for any of the 
genes on Mayo Clinic Laboratories’ (MCL) test menu. In addition, genes not on the MCL test menu 
may be able to be tested. Call the laboratory at 800-533-1710 with specific inquiries.

**Useful For:** Diagnostic or predictive testing for specific conditions when a DNA variant of interest 
has been previously identified in a family member and follow-up testing for this specific variant in other 
family members is desired. Carrier screening for individuals at risk for having a variant that was 
previously identified in a family member. Segregation analysis for a familial DNA variant. Confirmation 
germine status for variants detected via somatic testing.

**Interpretation:** Evaluation and categorization of variants is performed using American College of 
Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on 
known, predicted, or possible pathogenicity and reported with interpretive comments detailing their 
potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:** 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the 
interpretation of sequence variants: a joint consensus recommendation of the American College of 
Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 
May;17(5):405-424

**FANCP**

**Fanconi Anemia C Mutation Analysis, IVS4(+4)A->T and 
322delG, Varies**

**Clinical Information:** Fanconi anemia is an aplastic anemia that leads to bone marrow failure and 
myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, 
lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. The 
proteins encoded by the genes associated with Fanconi anemia may work together to repair DNA 
damage. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, 
IVS4(+4)A->T in the FANCC gene has been shown to be common in the Ashkenazi Jewish population. 
The carrier rate in the Ashkenazi Jewish population is 1 in 89 and the detection rate for this mutation 
using this assay is greater than 99%. A second FANCC mutation, 322delG, is overrepresented in 
patients of Northern European ancestry.

**Useful For:** Carrier screening for Fanconi anemia in individuals of Ashkenazi Jewish ancestry 
Prenatal diagnosis of Fanconi anemia in at-risk pregnancies. Confirmation of suspected clinical 
diagnosis of Fanconi anemia in individuals of Ashkenazi Jewish ancestry.
**FASC 70431**

**Fascin Immunostain, Technical Component Only**

**Clinical Information:** Fascin is an actin-bundling protein that is present in antigen-presenting cells and is upregulated in Epstein Barr virus-positive lymphocytes and Hodgkin cells. Antibodies to fascin result in distinct cytoplasmic staining of the Langerhans cells, follicular dendritic cells, and interdigitating reticulum cells in normal lymph nodes. Fascin is usually positive in classical Hodgkin lymphoma and negative in lymphocyte predominant Hodgkin lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**FATF 607701**

**Fat, Feces**

**Clinical Information:** Total fecal lipids include glycerides, phospholipids, glycolipids, soaps, sterols, cholesteryl esters, and sphingolipids. Excess fecal fat in feces, (steatorrhea) is indicative of malabsorption disorders, such as pancreatic insufficiency or Whipple disease. Therefore, measurement of the fecal fats can be useful in establishing a diagnosis of such pancreatic diseases as cystic fibrosis, chronic pancreatitis, neoplasia, or stone obstruction, and such intestinal diseases as Whipple disease, regional enteritis, tuberculous enteritis, gluten-induced enteropathy (also called celiac disease or sprue), and the atrophy of malnutrition. Distinguishing free fatty acids from neutral fats, once thought to be helpful in the differential diagnosis of pancreatic disease, has fallen out of favor. Note that the composition of fats in the feces, normally predominately free fatty acids, can change significantly to predominately neutral fatty acids when the patient is on orlistat. This test does not distinguish between free and neutral fatty acids.

**Useful For:** Diagnosing fat malabsorption due to pancreatic or intestinal disorders Monitoring effectiveness of enzyme supplementation in certain malabsorption disorders This test is not useful for differentiating among pancreatic diseases.

**Interpretation:** Excretion of more than 7 grams fat/24 hours, when on a diet of 100 to 150 g of fat, is suggestive of a malabsorption defect. Abnormal results from a random specimen should be confirmed by submission of a timed collection. Test values for timed fecal fat collections will be reported in terms of g/24 hours; the duration of the collection may be 24, 48, 72, or 96 hours. Test values for random fecal fat collections will be reported in terms of percent fat. Coefficient of Fat Absorption (CFA) can be calculated...
as follows: \[(\text{grams fat consumed} - \text{grams of fat excreted}) \times 100 \div \text{grams of fat consumed}\]

**Reference Values:**
**TIMED COLLECTION**
> or =18 years: 2-7 g fat/24 hours
Reference values have not been established for patients who are <18 years of age.

**RANDOM COLLECTION**
All ages: 0-19% fat

**Clinical References:**

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**Fatty Acid Oxidation Gene Panel, Varies**

**Clinical Information:** Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation. Disorders of fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy, skeletal myopathy, and cardiomyopathy. Most FAO disorders have a similar presentation and their biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens such as urine organic acids, plasma acylcarnitines, and fatty acids are influenced by dietary factors and the clinical status of the patient. This often leads to incomplete diagnostic information, or even false-negative results. Enzyme assays are limited to one enzyme per assay, which doesn’t allow for comprehensive testing for all FAO disorders. A comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features, given the broad clinical spectrum and genetic heterogeneity of FAO disorders. Acylcarnitine profile in plasma (ACRN / Acylcarnitines, Quantitative, Plasma) and urine organic acids (OAU / Organic Acids Screen, Urine) are the recommended first-tier tests to assess individuals for a FAO disorder. Additional testing includes an assay in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture), which is useful following molecular testing to determine whether variants of uncertain significance are pathogenic. The purpose of the in vitro probe assay is to offer screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions using fibroblast cultures.

**Useful For:** Follow up for abnormal biochemical results suggestive of a fatty acid oxidation disorder
Establishing a molecular diagnosis for patients with a fatty acid oxidation disorder
Identifying variants within genes known to be associated with a fatty acid oxidation disorder, allowing for predictive testing of at-risk family members

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Fatty Acid Oxidation Probe Assay, Fibroblast Culture

Clinical Information: Mitochondrial fatty acid beta-oxidation plays an important role in energy production during periods of fasting. When the body’s supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. Disorders of fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy, skeletal myopathy, and cardiomyopathy. Most FAO disorders have a similar presentation and their biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens such as urine organic acids, plasma acylcarnitines, and fatty acids are influenced by dietary factors and the clinical status of the patient. This can lead to incomplete diagnostic information or even false-negative results. The purpose of the in vitro probe assay is to offer screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions using fibroblast cultures.

Useful For: In vitro confirmation of biochemical diagnoses of the following fatty acid oxidation disorders: - Short-chain acyl-CoA dehydrogenase (SCAD) deficiency - Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency - Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency - Trifunctional protein deficiency - Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency - Carnitine palmitoyl transferase deficiency type II (CPT-II) - Carnitine-acylcarnitine translocase (CACT) deficiency

Confirmation of the following organic acid disorders: - 2-Methylbutyryl-CoA dehydrogenase (SBCAD) deficiency - Isobutyryl-CoA dehydrogenase (IBD) deficiency

This test is not useful for prenatal testing. This assay is not informative if the deficient enzyme is physiologically not expressed in skin fibroblasts.

Interpretation: Abnormal results will include a description of the abnormal profile in comparison to normal and abnormal controls. In addition, the concentration of those acylcarnitine species that abnormally accumulated in the cell medium are provided and compared to the continuously updated reference range based on analysis of normal controls. Interpretations of abnormal acylcarnitine profiles also include information about the results' significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies if indicated, name and phone number of contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring provider has additional questions.

Reference Values: An interpretive report will be provided.

inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. The Academy of Nutrition and Dietetics recommends that dietary fat for the healthy adult population should provide 20% to 35% of energy, with an increased consumption of n-3 polyunsaturated fatty acids and limited intake of saturated and trans fats. (1) Fatty Acid Oxidation (FAO) Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies thorough a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with FAO disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing for many of the FAO disorders is also available via FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very-long-chain fatty acids (VLCFA), alpha-oxidation of phytic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact, but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy via molecular genetic analysis is available; see XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies.

**Useful For:** Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

**Interpretation:** An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acidoxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of phytanic acid (along with normal pristanic acid concentrations) are seen in the Refsum disease (phytanase deficiency). Phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanic acid, and piperolic acid, allows differential diagnosis of peroxisomal disorders.
**Reference Values:**

**Octanoic Acid, C8:0**
- <1 year: 7-63 nmol/mL
- 1-17 years: 9-41 nmol/mL
- > or =18 years: 8-47 nmol/mL

**Decenoic Acid, C10:1**
- <1 year: 0.8-4.8 nmol/mL
- 1-17 years: 1.6-6.6 nmol/mL
- > or =18 years: 1.8-5.0 nmol/mL

**Decanoic Acid, C10:0**
- <1 year: 2-62 nmol/mL
- 1-17 years: 3-25 nmol/mL
- > or =18 years: 2-18 nmol/mL

**Lauroleic Acid, C12:1**
- <1 year: 0.6-4.8 nmol/mL
- 1-17 years: 1.3-5.8 nmol/mL
- > or =18 years: 1.4-6.6 nmol/mL

**Lauric Acid, C12:0**
- <1 year: 6-190 nmol/mL
- 1-17 years: 5-80 nmol/mL
- > or =18 years: 6-90 nmol/mL

**Tetradecadienoic Acid, C14:2**
- <1 year: 0.3-6.5 nmol/mL
- 1-17 years: 0.2-5.8 nmol/mL
- > or =18 years: 0.8-5.0 nmol/mL

**Myristoleic Acid, C14:1**
- <1 year: 1-46 nmol/mL
- 1-17 years: 1-31 nmol/mL
- > or =18 years: 3-64 nmol/mL

**Myristic Acid, C14:0**
- <1 year: 30-320 nmol/mL
- 1-17 years: 40-290 nmol/mL
- > or =18 years: 30-450 nmol/mL

**Hexadecadienoic Acid, C16:2**
- <1 year: 4-27 nmol/mL
- 1-17 years: 3-29 nmol/mL
- > or =18 years: 10-48 nmol/mL

**Hexadecenoic Acid, C16:1w9**
- <1 year: 21-69 nmol/mL
- 1-17 years: 24-82 nmol/mL
- > or =18 years: 25-105 nmol/mL

**Palmitoleic Acid, C16:1w7**
- <1 year: 20-1,020 nmol/mL
- 1-17 years: 100-670 nmol/mL
- > or =18 years: 110-1,130 nmol/mL

**Palmitic Acid, C16:0**
- <1 year: 720-3,120 nmol/mL
<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>&lt; 1 year</th>
<th>&lt; 1 year</th>
<th>&lt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-17 years: 960-3,460 nmol/mL</td>
<td>9-130 nmol/mL</td>
<td>16-150 nmol/mL</td>
<td></td>
</tr>
<tr>
<td>&gt; or = 18 years: 1,480-3,730 nmol/mL</td>
<td>9-130 nmol/mL</td>
<td>16-150 nmol/mL</td>
<td></td>
</tr>
<tr>
<td>Gamma-Linolenic Acid, C18:3w6</td>
<td>6-110 nmol/mL</td>
<td>9-130 nmol/mL</td>
<td>16-150 nmol/mL</td>
</tr>
<tr>
<td>Alpha-Linolenic Acid, C18:3w3</td>
<td>10-190 nmol/mL</td>
<td>20-120 nmol/mL</td>
<td>50-130 nmol/mL</td>
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<tr>
<td>Linoleic Acid, C18:2w6</td>
<td>350-2,660 nmol/mL</td>
<td>1,000-3,300 nmol/mL</td>
<td>1,600-3,500 nmol/mL</td>
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<tr>
<td>Oleic Acid, C18:1w9</td>
<td>250-3,500 nmol/mL</td>
<td>350-3,500 nmol/mL</td>
<td>650-3,500 nmol/mL</td>
</tr>
<tr>
<td>Vaccenic Acid, C18:1w7</td>
<td>140-720 nmol/mL</td>
<td>320-900 nmol/mL</td>
<td>280-740 nmol/mL</td>
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<tr>
<td>Stearic Acid, C18:0</td>
<td>270-1,140 nmol/mL</td>
<td>280-1,170 nmol/mL</td>
<td>590-1,170 nmol/mL</td>
</tr>
<tr>
<td>EPA, C20:5w3</td>
<td>2-60 nmol/mL</td>
<td>8-90 nmol/mL</td>
<td>14-100 nmol/mL</td>
</tr>
<tr>
<td>Arachidonic Acid, C20:4w6</td>
<td>110-1,110 nmol/mL</td>
<td>350-1,030 nmol/mL</td>
<td>520-1,490 nmol/mL</td>
</tr>
<tr>
<td>Mead Acid, C20:3w9</td>
<td>8-60 nmol/mL</td>
<td>3-24 nmol/mL</td>
<td>7-30 nmol/mL</td>
</tr>
<tr>
<td>Homo-Gamma-Linolenic Acid, C20:3w6</td>
<td>30-170 nmol/mL</td>
<td>60-220 nmol/mL</td>
<td>50-250 nmol/mL</td>
</tr>
<tr>
<td>Arachidic Acid, C20:0</td>
<td>30-120 nmol/mL</td>
<td>30-90 nmol/mL</td>
<td>50-90 nmol/mL</td>
</tr>
</tbody>
</table>
DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
> or =1 year: 4-13 nmol/mL

Docosanoic Acid, C22:0
0.0-96.3 nmol/mL

Nervonic Acid, C24:1
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Tetracosanoic Acid, C24:0
0.0-91.4 nmol/mL

Hexacosanoic Acid, C26:1
<1 year: 0.2-2.1 nmol/mL
> or =1 year: 0.3-0.7 nmol/mL

Hexacosanoic Acid, C26:0
0.00-1.30 nmol/mL

Pristanic Acid, C15:0(CH3)4
< or =4 months: 0.00-0.60 nmol/mL
5-8 months: 0.00-0.84 nmol/mL
9-12 months: 0.00-0.77 nmol/mL
13-23 months: 0.00-1.47 nmol/mL
> or =2 years: 0.00-2.98 nmol/mL

Phytanic Acid, C16:0(CH3)4
< or =4 months: 0.00-5.28 nmol/mL
5-8 months: 0.00-5.70 nmol/mL
9-12 months: 0.00-4.40 nmol/mL
13-23 months: 0.00-8.62 nmol/mL
> or =2 years: 0.00-9.88 nmol/mL

Triene/Tetraene Ratio

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 1018
### Total Saturated Acid

- **<1 year:** 1.2-4.6 mmol/L
- **1-17 years:** 1.4-4.9 mmol/L
- **> or =18 years:** 2.5-5.5 mmol/L

### Total Monounsaturated Acid

- **<1 year:** 0.3-4.6 mmol/L
- **1-17 years:** 0.5-4.4 mmol/L
- **> or =18 years:** 1.3-5.8 mmol/L

### Total Polyunsaturated Acid

- **<1 year:** 1.1-4.9 mmol/L
- **1-17 years:** 1.7-5.3 mmol/L
- **> or =18 years:** 3.2-5.8 mmol/L

### Total w3

- **<1 year:** 0.0-0.4 mmol/L
- **1-17 years:** 0.1-0.5 mmol/L
- **> or =18 years:** 0.2-0.5 mmol/L

### Total w6

- **<1 year:** 0.9-4.4 mmol/L
- **1-17 years:** 1.6-4.7 mmol/L
- **> or =18 years:** 3.0-5.4 mmol/L

### Clinical References:


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**FAPCP 82042 Fatty Acid Profile, Comprehensive (C8-C26), Serum**

**Clinical Information:** Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. The Academy of Nutrition and Dietetics recommends that dietary fat for the healthy adult population should provide 20% to 35% of energy, with an increased consumption of n-3 polyunsaturated fatty acids and limited intake.
of saturated and trans fats. (1) Fatty Acid Oxidation Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies through a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with fatty acid oxidation (FAO) disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the work-up and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing via the FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis are also available for many of the FAO disorders at Mayo Clinic Laboratories. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact, but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy via molecular genetic analysis is available; see XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies.

Useful For: Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

Interpretation: An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of serum very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of serum phytanic acid (along with normal pristanic acid concentrations) are seen in the Refsum disease (phytanase deficiency). Serum phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanoic acid and pipecolic acid allow differential diagnosis of peroxisomal disorders.

Reference Values:

Octanoic Acid, C8:0
- <1 year: 7-63 nmol/mL
- 1-17 years: 9-41 nmol/mL
- > or =18 years: 8-47 nmol/mL

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- <1 year: 0.8-4.8 nmol/mL
- 1-17 years: 1.6-6.6 nmol/mL
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Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
<1 year: 1-46 nmol/mL
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Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
> or =1 year: 7-30 nmol/mL

Homo-Gamma-Linolenic Acid, C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL
### DPA, C22:5w3
- **<1 year**: 6-110 nmol/mL
- **1-17 years**: 30-270 nmol/mL
- **≥18 years**: 20-210 nmol/mL

### DTA, C22:4w6
- **<1 year**: 2-50 nmol/mL
- **1-17 years**: 10-40 nmol/mL
- **≥18 years**: 10-80 nmol/mL

### Docosenoic Acid, C22:1
- **<1 year**: 2-20 nmol/mL
- **≥1 year**: 4-13 nmol/mL

### Docosanoic Acid, C22:0
- **0.0-96.3 nmol/mL**

### Nervonic Acid, C24:1
- **<1 year**: 30-150 nmol/mL
- **1-17 years**: 50-130 nmol/mL
- **≥18 years**: 60-100 nmol/mL

### Tetracosanoic Acid, C24:0
- **0.0-91.4 nmol/mL**

### Hexacosanoic Acid, C26:0
- **0.0-1.30 nmol/mL**

### Pristanic Acid, C15:0(CH3)4
- **< or =4 months**: 0.00-0.60 nmol/mL
- **5-8 months**: 0.00-0.84 nmol/mL
- **9-12 months**: 0.00-0.77 nmol/mL
- **13-23 months**: 0.00-1.47 nmol/mL
- **≥2 years**: 0.00-2.98 nmol/mL

### Phytanic Acid, C16:0(CH3)4
- **< or =4 months**: 0.00-5.28 nmol/mL
- **5-8 months**: 0.00-5.70 nmol/mL
- **9-12 months**: 0.00-4.40 nmol/mL
- **13-23 months**: 0.00-8.62 nmol/mL
- **≥2 years**: 0.00-9.88 nmol/mL

### Triene/Tetraene Ratio
- **< or =31 days**: 0.017-0.083
- **32 days-17 years**: 0.013-0.050
- **≥18 years**: 0.010-0.038

### Total Saturated Acid
- **<1 year**: 1.2-4.6 mmol/L
- **1-17 years**: 1.4-4.9 mmol/L
- **≥18 years**: 2.5-5.5 mmol/L

### Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

Clinical References:

PFAPE 60464

Fatty Acid Profile, Essential, Plasma

Clinical Information: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. The Academy of Nutrition and Dietetics recommends that dietary fat for the healthy adult population should provide 20% to 35% of energy, with an increased consumption of n-3 polyunsaturated fatty acids and limited intake of saturated and trans fats.(1)

Useful For: Evaluating the nutritional intake and intestinal absorption of essential fatty acids using plasma specimens Identifying deficiency of essential and other nutritionally beneficial fatty acids Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)

Interpretation: Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency
Reference Values:
Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
1-17 years: 7-30 nmol/mL
> or =18 years: 7-30 nmol/mL

Homo-Gamma-Linolenic C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
1-17 years: 4-13 nmol/mL
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050

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> or ≥ 18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or ≥ 18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or ≥ 18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or ≥ 18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or ≥ 18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or ≥ 18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or ≥ 18 years: 7.3-16.8 mmol/L

Clinical References:

FAPEP 82426

Fatty Acid Profile, Essential, Serum

Clinical Information: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones.

Useful For: Evaluating the nutritional intake and intestinal absorption of essential fatty acids using serum specimens Identifying deficiency of essential and other nutritionally beneficial fatty acids Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)
**Interpretation:** Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency.

**Reference Values:**

Lauric Acid, C12:0  
<1 year: 6-190 nmol/mL  
1-17 years: 5-80 nmol/mL  
> or =18 years: 6-90 nmol/mL

Myristic Acid, C14:0  
<1 year: 30-320 nmol/mL  
1-17 years: 40-290 nmol/mL  
> or =18 years: 30-450 nmol/mL

Hexadecenoic Acid, C16:1w9  
<1 year: 21-69 nmol/mL  
1-17 years: 24-82 nmol/mL  
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7  
<1 year: 20-1,020 nmol/mL  
1-17 years: 100-670 nmol/mL  
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0  
<1 year: 720-3,120 nmol/mL  
1-17 years: 960-3,460 nmol/mL  
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6  
<1 year: 6-110 nmol/mL  
1-17 years: 9-130 nmol/mL  
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3  
<1 year: 10-190 nmol/mL  
1-17 years: 20-120 nmol/mL  
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6  
< or =31 days: 350-2,660 nmol/mL  
32 days-11 months: 1,000-3,300 nmol/mL  
1-17 years: 1,600-3,500 nmol/mL  
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9  
<1 year: 250-3,500 nmol/mL  
1-17 years: 350-3,500 nmol/mL  
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7  
<1 year: 140-720 nmol/mL  
1-17 years: 320-900 nmol/mL  
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0  
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
1-17 years: 7-30 nmol/mL
> or =18 years: 7-30 nmol/mL

Homo-Gamma-Linolenic C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidonic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
1-17 years: 4-13 nmol/mL
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL
Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing for many of the FAO disorders is also available via FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis.

**Useful For:** Biochemical diagnosis of inborn errors of mitochondrial fatty acid oxidation, including deficiencies of medium-chain acyl-Co-A dehydrogenase, long-chain 3-hydroxyacyl-Co-A dehydrogenase, very long-chain acyl-Co-A dehydrogenase, and glutaric acidemia type 2

**Interpretation:** Fatty acid oxidation disorders are recognized on the basis of disease-specific metabolite patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines).

**Reference Values:**

Octanoic Acid, C8:0
- <1 year: 7-63 nmol/mL
- 1-17 years: 9-41 nmol/mL
- ≥18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
- <1 year: 0.8-4.8 nmol/mL
- 1-17 years: 1.6-6.6 nmol/mL
- ≥18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
- <1 year: 2-62 nmol/mL
- 1-17 years: 3-25 nmol/mL
- ≥18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
- <1 year: 0.6-4.8 nmol/mL
- 1-17 years: 1.3-5.8 nmol/mL
- ≥18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
- <1 year: 6-190 nmol/mL
- 1-17 years: 5-80 nmol/mL
- ≥18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
- <1 year: 0.3-6.5 nmol/mL
- 1-17 years: 0.2-5.8 nmol/mL
- ≥18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
- <1 year: 1-46 nmol/mL
- 1-17 years: 1-31 nmol/mL
- ≥18 years: 3-64 nmol/mL

Myristic Acid, C14:0
- <1 year: 30-320 nmol/mL
- 1-17 years: 40-290 nmol/mL
- ≥18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
- <1 year: 4-27 nmol/mL
- 1-17 years: 3-29 nmol/mL
- ≥18 years: 10-48 nmol/mL

Palmitoleic Acid, C16:1w7
Fatty Acid Profile, Peroxisomal (C22-C26), Plasma

Clinical Information: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders that are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects males; however, some females who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa,
neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, piperolic acid (PIPA / Pipecolic Acid, Serum; PIPU / Pipecolic Acid, Urine), phytanic acid and its metabolite pristanic acid. In addition, confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies) via molecular genetic analysis is available at Mayo Clinic Laboratories.

**Useful For:** Evaluating patients with possible peroxisomal disorders, including peroxisomal biogenesis disorders, X-linked adrenoleukodystrophy, and Refsum disease using plasma specimens

**Aiding in the assessment of peroxisomal function**

**Interpretation:** Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0, and phytanic acid/pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, we also include the calculated value of a discriminating function used to more accurately segregate hemizygous individuals from normal controls. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

**Reference Values:**

**C22:0**

< or = 96.3 nmol/mL

**C24:0**

< or = 91.4 nmol/mL

**C26:0**

< or = 1.30 nmol/mL

**C24:0/C22:0 RATIO**

< or = 1.39

**C26:0/C22:0 RATIO**

< or = 0.023

**PRISTANIC ACID**

- 0-4 months: < or = 0.77 nmol/mL
- 5-8 months: < or = 0.94 nmol/mL
- 9-12 months: < or = 1.47 nmol/mL
- 13-23 months: < or = 2.98 nmol/mL
- > or = 24 months: < or = 5.28 nmol/mL

**PHYTANIC ACID**

- 0-4 months: < or = 5.28 nmol/mL
- 5-8 months: < or = 5.50 nmol/mL
- 9-12 months: < or = 4.40 nmol/mL
- 13-23 months: < or = 8.62 nmol/mL
- > or = 24 months: < or = 9.88 nmol/mL

**PRISTANIC/PHYTANIC ACID RATIO**

- 0-4 months: < or = 0.28
- 5-8 months: < or = 0.28
9-12 months: < or =0.23
13-23 months: < or =0.24
> or =24 months: < or =0.39


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81369

Fatty Acid Profile, Peroxisomal (C22-C26), Serum

Clinical Information: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders that are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects males; however, some females who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, pipecolic acid (PIPA / Pipecolic Acid, Serum; PIPU / Pipecolic Acid, Urine), phytanic acid and its metabolite pristanic acid. In addition, confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies) via molecular genetic analysis is available at Mayo Clinic Laboratories.

Useful For: Evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy or peroxisomal biogenesis disorders (Zellweger syndrome spectrum) using serum specimens Aiding in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0, and phytanic acid:pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, serum phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of
peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, we also include the calculated value of a discriminating function used to more accurately segregate hemizygous individuals from normal controls. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

**Reference Values:**

- **C22:0**
  - $< \text{or} = 96.3 \text{nmol/mL}$

- **C24:0**
  - $< \text{or} = 91.4 \text{nmol/mL}$

- **C26:0**
  - $< \text{or} = 1.30 \text{nmol/mL}$

- **C24:0/C22:0 RATIO**
  - $< \text{or} = 1.39$

- **C26:0/C22:0 RATIO**
  - $< \text{or} = 0.023$

- **PRISTANIC ACID**
  - 0-4 months: $< \text{or} = 0.60 \text{nmol/mL}$
  - 5-8 months: $< \text{or} = 0.84 \text{nmol/mL}$
  - 9-12 months: $< \text{or} = 0.77 \text{nmol/mL}$
  - 13-23 months: $< \text{or} = 1.47 \text{nmol/mL}$
  - $> \text{or} = 24 \text{months:} < \text{or} = 2.98 \text{nmol/mL}$

- **PHYTANIC ACID**
  - 0-4 months: $< \text{or} = 5.28 \text{nmol/mL}$
  - 5-8 months: $< \text{or} = 5.70 \text{nmol/mL}$
  - 9-12 months: $< \text{or} = 4.40 \text{nmol/mL}$
  - 13-23 months: $< \text{or} = 8.62 \text{nmol/mL}$
  - $> \text{or} = 24 \text{months:} < \text{or} = 9.88 \text{nmol/mL}$

- **PRISTANIC/PHYTANIC ACID RATIO**
  - 0-4 months: $< \text{or} = 0.35$
  - 5-8 months: $< \text{or} = 0.28$
  - 9-12 months: $< \text{or} = 0.23$
  - 13-23 months: $< \text{or} = 0.24$
  - $> \text{or} = 24 \text{months:} < \text{or} = 0.39$

**Clinical References:**


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**FBN1B 64514**

**FBN1 Full Gene Sequence, Varies**

**Clinical Information:** Fibrillin-1 is a 320-kD cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils that provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the FBN1 gene, which contains 65 exons and is located at chromosome 15q21. Pathogenic FBN1 variants are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender
Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse. There is significant inter- and intrafamilial variability in the MFS phenotype. Pathogenic FBN1 variants have also been reported in several other rare phenotypes with variable overlap with classic MFS. In some cases, MFS may present in the neonatal period with severe, rapidly progressive disease (previously termed "neonatal Marfan syndrome"). Other FBN1-associated conditions include autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissection, isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis). Hundreds of pathogenic variants have been identified in FBN1, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among pathogenic FBN1 variants. Approximately two-thirds of pathogenic FBN1 variants are missense changes, with the majority of these being cysteine substitutions. Approximately 25% to 33% of pathogenic FBN1 variants are de novo, in which an individual has no family history of disease. Pathogenic FBN1 variants have been shown to occur across the gene. Some genotype-phenotype correlations have been observed, including the association with truncating and splicing variants with risk for aortic dissection, cysteine-based variants, and ectopia lentis, and severe, early onset MFS and variants in exons 24 through 32. Marfan syndrome has significant clinical overlap with a condition called Loeys-Dietz syndrome (LDS); however, the vascular phenotype of LDS can be more severe, and LDS is caused by pathogenic variants in different genes (TGFBR1, TGFBR2, SMAD3, and TGFBR2). When the diagnosis of MFS, LDS, or a related disorder is suspected, the use of genetic testing is important to verify the diagnosis and provide appropriate clinical management. Confirmation of the genetic diagnosis also allows for preconception, prenatal, and family counseling.

**Useful For:** Aiding in the diagnosis of: - FBN1-associated Marfan syndrome - Autosomal dominant ectopia lentis - Isolated ascending aortic aneurysm and dissection - Isolated skeletal features of Marfan syndrome - MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS) - Shprintzen-Goldberg syndrome - Autosomal dominant Weill-Marchesani syndrome

**Interpretation:** Evaluation and categorization of variants is performed using American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment. Unless reported or predicted to impact splicing, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported.

**Reference Values:** An interpretive report will be provided.

**Feather Panel # 2, Serum**

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Fecal Leukocytes, Feces**

**Clinical Information:** Leukocytes are not normally seen in feces in the absence of infection or other inflammatory processes. Fecal leukocytosis is a response to infection with microorganisms that invade tissue or produce toxins, which causes tissue damage. Fecal leukocytes are commonly found in patients with shigellosis and salmonellosis and sometimes in amebiasis. Mononuclear cells are found in typhoid fever. Ulcerative colitis may also be associated with fecal leukocytosis.
Useful For: Suggesting the presence of pathogens such as Salmonella, Shigella, and amebiasis

Interpretation: When fecal leukocytes are found they are reported in a semiquantitative manner: "few" indicates \(<2/oil immersion microscopic field (OIF); "moderate" indicates 3-9/OIF; "many" indicates \(>10/OIF. The greater the number of fecal leukocytes, the greater the likelihood that an invasive pathogen such as Salmonella or Shigella is present. Few or no leukocytes and many erythrocytes suggests amebiasis. Fecal leukocytes are rarely seen in diarrheas caused by other parasites or viruses.

Reference Values:
Interpretive report


Fecal Occult Blood, Colorectal Cancer Screen, Qualitative, Immunochemical, Feces

Clinical Information: Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the United States, and the second leading cause of cancer-related deaths. CRC almost always develops from adenomatous polyps, yet patients remain asymptomatic until the cancer progresses to a fairly advanced stage. Screening for colorectal cancer is strongly advocated for by the United States Preventive Services Task Force, the American Cancer Society, the American College of Gastroenterology, and other clinical societies, due to the high incidence of disease and decrease in mortality with medical intervention. Men and women at average risk for colorectal cancer should be screened at regular intervals beginning at age 50 and continuing until age 75. Individuals with certain high-risk factors (age, African-American race, inflammatory intestinal disorders, family history of colon cancer, obesity, diabetes, poor diet) may consider earlier screening strategies. A variety of options are available for colorectal cancer screening including: fecal occult blood testing, sigmoidoscopy, colonoscopy, and multimarker Cologuard testing that includes genetic markers of colorectal cancer. Historically occult blood tests utilized guaiac-based tests that were susceptible to dietary interferences, but this test utilizes fecal immunochemical testing (FIT) specific for human hemoglobin, eliminating the need for dietary and medication restrictions. For colorectal cancer screening, only a single collection is required. The specificity of FIT is routinely greater than 95% with reported sensitivities ranging from 40% to 70% based on the patient population. The clinical specificity of FIT is 97% based on internal studies conducted at Mayo Clinic but can be limited by gastrointestinal bleeding from a non-colorectal cancer source. In a recent study of 10,000 average risk participants, Cologuard detected colorectal cancer, precancerous lesions, and polyps with high-grade dysplasia with higher sensitivity than FIT testing.(1) However, Cologuard had slightly lower specificity than FIT testing in that study. Cologuard requires an entire bowel movement for testing versus 1 small sample for FIT. Current societal guidelines endorse the use of FIT and Cologuard interchangeably with 1-year based screening for FIT versus a suggested 3-year DNA based screening for average risk population, recognizing that the testing interval for the latter is uncertain.(2,3)

Useful For: Colorectal cancer screening Screening for gastrointestinal bleeding This test has not been validated for testing of patients with hemoglobinopathies.

Interpretation: This is a quantitative assay but results are reported qualitatively as negative or positive for the presence of fecal occult blood; the cutoff for positivity is 100 ng/mL hemoglobin. The following comments will be reported with the qualitative result for patients older than 17 years: -Positive results; further testing is recommended if clinically indicated. This test has 97% specificity for detection of lower gastrointestinal bleeding in colorectal cancer. -Negative results; this test will not detect upper gastrointestinal bleeding; HQ / HemoQuant, Feces test should be ordered if clinically indicated.

Reference Values:
Negative

This test has not been validated in a pediatric population, results should be interpreted in the context of the patient's presentation.

FELBA 80782

Felbamate (Felbatol), Serum

Clinical Information: Felbamate is an anticonvulsant drug approved for treatment of partial seizures with or without secondary generalization in persons 14 years of age and older. It is also approved for Lennox-Gastout syndrome in children 2 years of age and older. Felbamate is well absorbed (>90%) and is metabolized by the hepatic cytochrome P450 system. Metabolites lack anticonvulsant activity. The elimination half-life of felbamate ranges from 13 to 23 hours. Optimal response to felbamate is seen with serum concentrations between 30 mcg/mL to 60 mcg/mL. Patients who are older adults or have renal dysfunction may require reduced dosing; felbamate should not be given to individuals with hepatic disease. Toxicity can be severe, including life-threatening aplastic anemia or liver failure; toxic concentration has been established at concentrations greater than 100 mcg/mL. Coadministration of felbamate increases the concentration of phenytoin and valproic acid, decreases carbamazepine concentration, and increases carbamazepine-10,11-epoxide (its active metabolite). Conversely, coadministration of phenytoin or carbamazepine causes a decrease in felbamate concentration.

Useful For: Determining whether a poor therapeutic response is attributable to noncompliance or lack of drug effectiveness Monitoring changes in serum concentrations resulting from interactions with coadministered drugs such as barbiturates and phenytoin

Interpretation: Optimal response to felbamate is associated with serum concentrations of 30 mcg/mL to 60 mcg/mL. Toxic serum concentrations for felbamate have been established at concentrations greater than 100 mcg/mL.

Reference Values: 30.0-60.0 mcg/mL

**Fentanyl and Metabolite, Chain of Custody, Serum**

**Clinical Information:** Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines. It is available in injectable as well as transdermal formulations. The analgesic effects of fentanyl is similar to those of morphine and other opioids; it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. Fentanyl is approximately 80% to 85% protein bound. Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. The average volume of distribution for fentanyl is 6 L/kg (range 3-8). In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug. The mean elimination half-life is: (1-3) - IV: 2 to 4 hours - Iontophoretic transdermal system (Ionsys), terminal half-life: 16 hours - Transdermal patch: 17 hours (range 103-22 hours, half-life is influenced by absorption rate) - Transmucosal: - Lozenge: 7 hours - Buccal tablet: - 100 mcg to 200 mcg: 3 to 4 hours - 400 mcg to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. In addition to analgesia, alterations in mood, euphoria, dysphoria, and drowsiness commonly occur. Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse. Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Monitoring fentanyl therapy Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Both fentanyl and norfentanyl are reported. Tolerant individuals may require many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate interpretation of therapeutic drug monitoring results and establishment of a therapeutic window. Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

**Reference Values:** Not applicable

**Clinical References:**

**Fentanyl Screen with Reflex, Random, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody. Because the ability to cross-react with different drugs in the class being screened for.

**Useful For:** Screening for drug abuse or use involving fentanyl
**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
Negative
Screening cutoff concentration:
Fentanyl: 2 ng/mL

**Clinical References:**

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**FENS**

**Fentanyl Screen, Random, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened for.

**Useful For:** Screening for drug abuse or use involving fentanyl

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
Negative
Screening cutoff concentration:
Fentanyl: 2 ng/mL

**Clinical References:**

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**FENTX**

**Fentanyl with Metabolite Confirmation, Chain of Custody, Random, Urine**

**Clinical Information:** Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 17 hours -Transdermal patch: 17 hours
Fentanyl with Metabolite Confirmation, Random, Urine

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines. (1, 2) It is available in injectable as well as transdermal formulations. (1) The analgesic effects of fentanyl are similar to those of morphine and other opioids: (1) it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue. (1, 3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8). (3, 4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. (3, 4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate) -Transmucosal: Â - Lozenge: 7 hours Â - Buccal tablet Â - 100 to 200 mcg: 3 to 4 hours Â - 400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur. (1, 3) Because the biological effects of fentanyl are similar to those of heroin and other opioids,
Fentanyl, Serum

**Clinical Information:** Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.\(^1,2\) It is available in injectable as well as transdermal formulations.\(^1\) The analgesic effects of fentanyl is similar to those of morphine and other opioids:\(^1\) it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.\(^1,3\) Fentanyl is approximately 80% to 85% protein bound.\(^1\) Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8).\(^3,4\) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug.\(^3,4\) The mean elimination half-life is: (1-3) -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys), terminal half-life: 16 hours -Transdermal patch: 17 hours (range 13-22 hours, half-life is influenced by absorption rate) -Transmucosal: -Lozenge: 7 hours -Buccal tablet -100 to 200 mcg: 3 to 4 hours -400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.\(^1,3\) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

**Useful For:** Monitoring fentanyl therapy

**Interpretation:** Both fentanyl and norfentanyl are reported. Tolerant individuals may require many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate interpretation of therapeutic drug monitoring results and establishment of a therapeutic window. Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

**Reference Values:**

Not applicable

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

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

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

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Ferritin, Serum

Clinical Information: Ferritin is a large spherical protein consisting of 24 noncovalently linked subunits with a molecular weight of approximately 450,000 D. The subunits form a shell surrounding a central core containing variable amounts of ferric hydroxyphosphate. One molecule of ferritin is capable of binding between 4000 and 5000 atoms of iron, making ferritin the major iron storage protein for the body. Ferritin is found chiefly in the cytoplasm of cells of the reticuloendothelial system and is a constituent of normal human serum. The concentration of ferritin is directly proportional to the total iron stores in the body, resulting in serum ferritin concentrations becoming a common diagnostic tool in the evaluation of iron status. In most normal adults, serum ferritin concentrations vary with age and sex. There is a sharp rise in serum ferritin concentrations in the first month of life, coinciding with the depression of bone marrow erythropoiesis. Within 2 or 3 months, erythropoiesis becomes reactivated and
there is a drop in the concentration of serum ferritin. By 6 months, the concentration is reduced to fairly low levels where they remain throughout childhood. There is no sex difference until the onset of puberty, at which time ferritin concentrations rise, particularly in males. There is a significant positive correlation between age and serum ferritin concentrations in females, but not in males. Patients with iron deficiency anemia have serum ferritin concentration approximately one-tenth of normal subjects, while patients with iron overload (hemochromatosis, hemosiderosis) have serum ferritin concentrations much higher than normal. Studies also suggest that serum ferritin provides a sensitive means of detecting iron deficiency at an early stage. Serum ferritin concentrations may serve as a tool to monitor the effects of iron therapy, but results should be interpreted with caution, as these cases may not always reflect the true state of iron stores. Ferritin is a positive acute phase reactant in both adults and children, whereby chronic inflammation results in a disproportionate increase in ferritin in relation to iron reserves. Elevated ferritin is also observed in acute and chronic liver disease, chronic renal failure, and in some types of neoplastic disease. Evaluating body iron stores may include serum iron determination, total iron binding capacity (TIBC), and percent saturation of transferrin, however are subject to diurnal variations and may be less precise. Additionally, they do not discriminate between depleted iron stores (iron deficiency) and conditions associated with defective iron release (eg, anemia of chronic disease).

**Useful For:** Aiding in the diagnosis of iron deficiency and iron overload conditions Differentiating iron deficiency anemia and anemia of chronic disease

**Interpretation:** Hypoferritinemia is associated with increased risk for developing iron deficiency where iron deficiency is sufficient to reduce erythropoiesis causing hemoglobin concentrations to fall. Latent iron deficiency occurs when serum ferritin is low without low hemoglobin. Hyperferritinemia is associated with iron overload conditions including hereditary hemochromatosis where concentrations may exceed 1000 mcg/L. Non-iron overload hyperferritinemia may be caused by common liver disorders, neoplasms, acute or chronic inflammation, and hereditary hyperferritinemia-cataract syndrome. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

**Reference Values:**
- Males: 24-336 mcg/L
- Females: 11-307 mcg/L

**Clinical References:**

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**Ferrochelatase (FECH) Gene, Full Gene Analysis, Varies**

**Clinical Information:** Erythropoietic protoporphyria (EPP) is an inherited disorder of porphyrin metabolism whose clinical manifestations include painful photodermatitis without blisters and liver disease. The disorder results from decreased activity of the enzyme ferrochelatase (FECH). FECH is the last of 8 enzymes acting sequentially in the heme biosynthetic pathway and is encoded by the FECH gene located on chromosome 18. The skin symptoms in EPP include immediate painful photosensitivity, usually beginning in early infancy upon sun exposure. Repeated photosensitivity episodes result in skin thickening and areas of hyperkeratosis. This is typically noted on areas where sun exposure is most common, such as the dorsa of the hands and on the face. A small number of patients with EPP develop liver complications. Hepatic disease in EPP may include cholelithiasis and chronic liver disease progressing to rapid acute liver failure. Biochemically, EPP is characterized by elevated protoporphyrin levels in red blood cells, which fluorescence under Wood’s light due to the accumulation of free protoporphyrin IX. Protoporphyrin elevations may also be found in plasma and stool, but not in all patients. Urine protoporphyrin levels are usually normal unless there is liver involvement. Studies have also suggested that a reduction in activity of ferrochelatase to <50% of normal levels can induce clinical manifestations. The gold standard test for the diagnosis of EPP is biochemical analysis (PEE / Porphyrins Evaluation, Whole Blood), interpreted in the context of clinical features. In most patients with EPP, a pathogenic FECH mutation that reduces enzyme activity by 50% can be identified on only 1 allele. Clinical expression of EPP typically requires a hypomorphic (low expression) FECH allele.
(IVS3-48T->C) in trans (on a different chromosome) with the mutation. IVS3-48T->C is a variant of the FECH gene associated with reduced gene expression. This variant is found in approximately 10% of the general Caucasian population. Autosomal recessive inheritance (2 pathogenic mutations in trans) is infrequent, accounting for <4% of EPP cases. In contrast to patients with 1 pathogenic mutation and the low-expression allele, missense mutations are far more common than null mutations. It is uncertain whether protoporphyric liver failure is more common among individuals with a single null (splicing defect, nonsense, or frameshift) mutation than those with 2 pathogenic mutations as some literature has suggested. In any case, it is certain that all EPP patients should be monitored for hepatic disease and actively manage their photosensitivity.

**Useful For:** Confirmation of a diagnosis of erythropoietic protoporphyria (EPP) following positive biochemical genetic test results obtained through PEE / Porphyrins Evaluation, Whole Blood Carrier testing for individuals with a family history of EPP in the absence of known mutations in the family

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Fetomaternal Bleed, Flow Cytometry, Blood**

**Clinical Information:** In hemolytic disease of the newborn, fetal red blood cells become coated with IgG alloantibody of maternal origin, which is directed against an antigen on the fetal cells that is of paternal origin and is absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red blood cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage (FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red blood cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen.(1) Rh immune globulin (RhIG, anti-D antibody) is given to Rh-negative mothers who are pregnant with a Rh-positive fetus. Anti-D antibody binds to fetal D-positive red blood cells, preventing development of the maternal immune response. RhIG can be given either before or after delivery. The volume of FMH determines the dose of RhIG to be administered.

**Useful For:** Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin

**Interpretation:** Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300 mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBC. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects.
The effectiveness of RhIG decreases beyond 72 hours post exposure but may still be clinically warranted. This assay has been validated out to 5 days post collection.

Reference Values:
< or =1.5 mL of fetal red blood cells in normal adults


Fetomaternal Bleed, New York, Blood

Clinical Information: In hemolytic disease of the newborn, fetal red blood cells become coated with IgG alloantibody of maternal origin, which is directed against an antigen on the fetal cells that is of paternal origin and is absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red blood cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage (FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red blood cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen. Rh immune globulin (RhIG, anti-D antibody) is given to Rh-negative mothers who are pregnant with a Rh-positive fetus. Anti-D antibody binds to fetal D-positive red blood cells, preventing development of the maternal immune response. RhIG can be given either before or after delivery. The volume of FMH determines the dose of RhIG to be administered.

Useful For: Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin. This test is used only for specimens collected in New York state.

Interpretation: Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300-mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBC. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects. The effectiveness of RhIG decreases beyond 72 hours postexposure but may still be clinically warranted. This assay has been validated out to 5 days post collection.

Reference Values:
< or =1.5 mL of fetal red blood cells in normal adults


FGFR Mutation and Fusion Analysis, Tumor

Clinical Information: As high as 32% of individuals with urothelial cancer have been observed to have an activating fibroblast growth factor receptor (FGFR) alteration and approximately half of those are in FGFR3. The FGFR isotypes are part of the RAS/MAPK, PI3K/AKT, PLCgamma, and STAT intracellular signaling pathways involved in cell proliferation and survival. FGFR mutations, primarily...
those occurring in the kinase domain, result in constitutive activation and contribute to tumorigenesis. The FGFR kinase inhibitor erdafitinib (BALVERSA) is a drug therapy approved by the FDA for individuals with FGFR3 and FGFR2-mutated advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy has become ineffective. Current data suggest that the efficacy of FGFR-targeted therapy in urothelial cancer is highest in patients with tumors demonstrating the presence of the FGFR3-activating mutations R248C, S249C, G370C, Y373C, and fusions FGFR3-TACC3v3, FGFR3-TACC3v1. As a result, the mutation status of FGFR is a critical marker for selecting patients for FGFR-targeted therapy. This FDA approved test uses RNA extracted from the tumor tissue to evaluate for the presence of mutations of R248C, S249C, G370C, and Y373C in the FGFR3 gene, as well as fusions FGFR3-TACC3v3 and FGFR3-TACC3v1. A positive result showing any of these alterations indicates the presence of an FGFR mutation and may be useful for guiding the treatment of individuals with urothelial cancer. This test was also designed to find fusions FGFR3-BAIAP2L1, FGFR2-BICC1, and FGFR2-CASP7. However, FDA approval of this assay to detect these fusions was not gained due to lack of patient samples. Drug efficacy and safety has not been established for these fusions, which were included in clinical trials. These fusions will be reported if detected but are considered off-label use of the test. At this time, this test is approved specifically for patients with urothelial cancer. The utilization of this test in patients with other tumor types could be considered an off-label use of this test.

**Useful For:** Identification of urothelial tumors that may respond to FGFR-targeted therapies. This test is not intended for use for hematological malignancies and does not assess germline alterations within the genes listed.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FGF1F**

**FGFR1 (8p11.2) Amplification, FISH, Tissue**

**Clinical Information:** Fibroblast growth factor receptor 1 (FGFR1) is a receptor tyrosine kinase. FGFR1 overexpression or amplification in squamous cell carcinoma is associated with tumor growth. Studies have shown overexpression or amplification of FGFR1 to be vulnerable to FGFR-tyrosine kinase inhibitors and FGFR1 inhibitors maybe a promising therapeutic option and have shown tumors with FGFR1 amplification may be sensitive to FGFR1 tyrosine kinase inhibitors.

**Useful For:** Providing prognostic information and guiding treatment primarily for patients with squamous cell carcinoma of the lung, breast, esophagus, thymus, and other locations

**Interpretation:** FGFR1 will be clinically interpreted as positive or negative. The FGFR1 locus is reported as amplified when the FGFR1:D8Z2 ratio is >2.0 or an average of 6 or more copies of the FGFR1 locus are observed per tumor nucleus. A tumor with an FGFR1:D8Z2 ratio < or =2.0 and having an average of <6 copies of FGFR1 per tumor nucleus is considered negative for amplification of the FGFR1 locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FGFR1 (8p11.2) Rearrangement, FISH**

**Clinical Information:** The gene for fibroblast growth factor receptor 1 (FGFR1) is located at 8p11.2 and rearrangements of FGFR1 are found in stem cell myeloproliferative disorders involving both lymphoid and myeloid lineages. The stem cell myeloproliferative disorders with FGFR1 rearrangements are also called 8p11 (eight p11) myeloproliferative syndromes (EMS) and have variable presentations. EMS often transform rapidly into myelomonocytic leukemia and generally have a poor outcome due to resistance to current chemotherapies, including imatinib mesylate; median survival is about 12 months. All translocations affecting FGFR1 have a similar structure with a 5' gene partner translocating to the 3' FGFR1 at exon 9. The fusion transcripts encode large proteins containing the N-terminus of the translocation partner, and the tyrosine kinase domain of FGFR1 in the C-terminus. Leukemogenesis is caused by inappropriate activation of FGFR1.

**Useful For:** An aid in identifying patients with myeloproliferative syndromes and the t(8;var)(p11.2;var) translocation who therefore are likely resistant to current chemotherapies

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
3. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. Edited by SH Swerdlow, E Campo, NL Harris, et al. Published by the InternationalAgency for Research on Cancer (IARC), 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, 2008, pp 72-73

**FGFR2 (10q26.1) Rearrangement, FISH, Tissue**

**Clinical Information:** Cholangiocarcinoma is a malignancy arising from the biliary tract epithelium. These tumors are often clinically advanced at the time of presentation and the prognosis is very poor with a short overall survival. Treatment is generally limited to surgical resection, which is associated with a high degree of morbidity, and palliative chemotherapy regimens. Therefore, additional treatment options are eagerly sought. Rearrangement of the FGFR2 gene region has been identified in a subset of cholangiocarcinomas. These rearrangements result in overexpression of FGFR2, which offers the possibility of using targeted FGFR2-inhibitor therapy for treatment. FGFR2 rearrangement has been identified in a number of other cancers including those of the bladder, thyroid, oral cavity, and brain. In the future, it is likely that the presence of FGFR2 rearrangements will be exploited in the treatment of these cancers as well.

**Useful For:** Providing prognostic information and guiding treatment for patients with cholangiocarcinomas and other tumor types including bladder, thyroid, oral cavity, and brain

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds
the normal cutoff for the probe set. A positive result suggests rearrangement of the FGFR2 locus and a tumor that may be responsive to targeted FGFR2-inhibitor therapy. A negative result suggests no rearrangement of the FGFR2 gene region at 10q26.1.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MSFGN**  
**Fibrillary Glomerulonephritis Confirmation, LC-MS/MS, Paraffin Tissue**

**Clinical Information:** Fibrillary glomerulonephritis (FGN) is a rare kidney disease with fibrillary deposits in the glomeruli that contain polyclonal IgG and complement, indicating immune complex deposition. Although usually Congo-red negative, recently cases with weak Congo-red positivity have been observed, making the distinction from amyloid more challenging. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) performed on microdissected glomeruli from patients with FGN demonstrates a unique proteomic profile including the protein DNAJB9 (Mayo Clinic unpublished observations). The presence of DNAJB9 was found to be highly sensitive and specific for FGN, distinguishing it from other glomerular diseases including amyloid, immunotactoid glomerulopathy, and immune complex-mediated proliferative glomerulonephritis. The presence of DNAJB9, in the appropriate clinical and pathological context, can be useful to establish a diagnosis of FGN.

**Useful For:** Diagnosis of fibrillary glomerulonephritis

**Interpretation:** An interpretation will be provided.

**Clinical References:**

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**FGAZ**  
**Fibrinogen Alpha-Chain (FGA) Gene, Full Gene Analysis, Varies**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been...
associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, gelsolin, cystatin C, lysozyme, and fibrinogen alpha chain (FGA). Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as nonneuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. FGA-related familial visceral amyloidosis commonly presents with renal failure, which can often be fulminant, and is characterized by hypertension, proteinuria, and azotemia. Liver and spleen involvement may be seen in advanced cases. Neuropathy is not a feature of FGA-related familial visceral amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions.

Tissue-based, laser-capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clinically clear. It is important to note that there are rare disorders of hemostasis that are also associated with mutations in the FGA gene. Patients with afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia have all been reported to have mutations in FGA. Most dysfibrinogenemias are autosomal dominant disorders; afibrinogenemia and hypofibrinogenemia are more often autosomal recessive disorders. In general, truncating mutations in FGA result in afibrinogenemia and missense mutations are a common cause of dysfibrinogenemia.

**Useful For:** Confirming a diagnosis of fibrinogen alpha-chain (FGA) gene-related familial visceral amyloidosis

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FIBAG**

**Fibrinogen Antigen, Plasma**

**Clinical Information:** Fibrinogen (clotting factor I) is an essential protein responsible for blood clot formation. In the final step of the coagulation cascade, thrombin converts soluble fibrinogen into insoluble fibrin strands that crosslink and form a clot. Fibrinogen is synthesized in the liver and has a biological half-life of 3 to 5 days in the circulating plasma. Fibrinogen deficiencies can be congenital or acquired and lead to prolonged coagulation times. Isolated fibrinogen deficiency is an extremely rare inherited coagulation disorder. Acquired fibrinogen deficiency is most commonly caused by, acute or decompensated intravascular coagulation and fibrinolysis (DIC). Other causes of fibrinogen deficiency include advanced liver disease, L-asparaginase therapy, or fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator).

**Useful For:** Evaluation of fibrinogen deficiency Measuring fibrinogen in patients with elevated plasma levels of fibrin degradation products, patients receiving heparin, and in patients with antibodies to thrombin (following surgical use of topical bovine thrombin) Identifying afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia when ordered in combination with fibrinogen activity (FIB / Fibrinogen,Plasma)

**Interpretation:** This method measures the total amount of fibrinogen protein (ie, fibrinogen antigen) present in the plasma. Adequate fibrinogen antigen levels in a context of low fibrinogen activity
suggests a dysfibrinogenemia. Fibrinogen antigen levels <100 mg/dL are associated with an increased risk of bleeding.

**Reference Values:**
196-441 mg/dL


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**Fibrinogen, Clauss, Plasma**

**Clinical Information:** Fibrinogen, also known as factor 1, is a plasma protein that can be transformed by thrombin into a fibrin gel ("the clot"). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely than the acquired to be associated with bleeding or thrombotic disorders. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Congenital dysfibrinogenemias usually are inherited as autosomal codominant traits. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or renal diseases associated with elevated fibrinogen levels. Fibrinogen is an acute-phase reactant, so a number of acquired conditions can result in an increase in its plasma level: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial and venous thromboembolism.

**Useful For:** Detecting increased or decreased fibrinogen (factor 1) concentration of acquired or congenital origin Monitoring severity and treatment of disseminated intravascular coagulation and fibrinolysis

**Interpretation:** This test assesses levels of functional (clottable) fibrinogen (see Cautions). Fibrinogen may be decreased in acquired conditions such as liver disease and acute intravascular coagulation and fibrinolysis and disseminated intravascular coagulation (ICF/DIC). Fibrinogen may be decreased in rare conditions including congenital afibrinogenemia or hypofibrinogenemia. Fibrinogen may be elevated with acute or chronic inflammatory conditions.

**Reference Values:**
Only orderable as part of a profile or reflex. For more information, see:
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- APROL / Prolonged Clot Time Profile, Plasma
- AATHR / Thrombophilia Profile, Plasma
- ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma
- ALUPP / Lupus Anticoagulant Profile, Plasma

Males: 200-500 mg/dL
Females: 200-500 mg/dL

In normal full-term newborns and in healthy premature infants (30-36 weeks gestation) fibrinogen is near adult levels (>150) and reaches adult levels by <21 days postnatal.

**Clinical References:**
1. Dang CV, Bell WR, Shuman M: The normal and morbid biology of
Fibrinogen, Plasma

**Clinical Information:** Fibrinogen, also known as factor I, is a plasma protein that can be transformed by thrombin into a fibrin gel ("the clot"). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation: DIC), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely to be associated with bleeding or thrombotic disorders than the acquired dysfibrinogenemias are. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or kidney diseases (eg, chronic glomerulonephritis, hypernephroma) and usually are associated with elevated fibrinogen levels. Fibrinogen is an acute phase reactant, so a number of acquired conditions can result in an increase in its plasma concentration: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation -Diabetes -Obesity The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial thromboembolism.

**Useful For:** Detecting increased or decreased fibrinogen (factor I) concentration of acquired or congenital origin Monitoring severity and treatment of disseminated intravascular coagulation and fibrinolysis

**Interpretation:** Fibrinogen may be decreased in acquired conditions such as liver disease and acute intravascular coagulation and fibrinolysis and disseminated intravascular coagulation (ICF/DIC). Fibrinogen may be decreased in rare conditions including congenital afibrinogenemia or hypofibrinogenemia. Fibrinogen may be elevated with acute or chronic inflammatory conditions.

**Reference Values:**
200-393 mg/dL


Fibroblast Culture for Genetic Testing, Tissue

**Clinical Information:** Fibroblast cells may be used to perform a wide range of laboratory tests. Prior to testing, the tissue may need to be cultured to obtain adequate numbers of cells.

**Useful For:** Producing fibroblast cultures that can be used for genetic analysis
**Reference Values:**
Not applicable


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**FIBR 8482**

**Fibroblast Culture, Tissue**

**Clinical Information:** Cultures of skin fibroblasts are useful for specialized tests requiring skin cells. These cells can be cultured and tested at Mayo Clinic or sent to external laboratories performing these specialized tests. In addition, cells are frozen for a minimum of 3 years for potential future studies on cultured cells or for molecular genetic testing.

**Useful For:** Obtaining cultured cells for specialized testing including enzymatic and molecular genetic

**Reference Values:**
Not applicable

**Clinical References:**

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**FGFRC 71483**

**Fibroblast Growth Factor Receptor 1 IHC, Technical Component Only**

**Clinical Information:** Fibroblast growth factor receptor 1 (FGFR1) is a receptor tyrosine kinase that belongs to the fibroblast growth factor family. FGFR1 amplification is seen in 13% to 22% of lung squamous cell carcinoma (SQCC) and has been associated with a worse prognosis.

**Useful For:** Classification of a subset of lung squamous cell carcinoma

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**PRKAF 64777**

**Fibrolamellar Carcinoma, 19p13.1 (PRKACA) Rearrangement, FISH, Tissue**

**Clinical Information:** DNAJB1-PRKACA fusion has been associated with a distinct subtype of hepatocellular carcinoma called fibrolamellar carcinoma. A break-apart strategy FISH probe has been developed to detect the rearrangement event that occurs in the DNAJB1-PRKACA fusion, specifically the loss of the 5’ region labeled in red and retention of the 3’ region labeled in green.

**Useful For:** Aid in the diagnosis of identifying PRKACA gene rearrangements of patients with fibrolamellar carcinoma

**Interpretation:** A positive result with the PRKACA probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of PRKACA suggests fusion
of the PRKACA and DNAJB1 genes at 19p13.1. A negative result suggests no fusion of the PRKACA and DNAJB1 genes has occurred.

**Reference Values:**
An interpretive report will be provided.


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**FibroTest-ActiTest, Serum**

**Clinical Information:** Fibrosis and inflammatory activity are the 2 main causes of liver disease. FibroTest-ActiTest estimates the levels of fibrosis and cirrhosis in the liver as well as the level of necroinflammatory activity. The estimation is made by measuring 6 standard serum biomarkers (gamma-glutamyl transferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, and alanine aminotransferase). The activity score is a measure of liver inflammation caused by disease. Results from these tests are combined with the patient’s age and sex to estimate hepatic fibrosis and inflammatory activity scores. Hepatic fibrosis is typically compared to a form of scar tissue that progresses throughout the liver. The most serious stage of fibrosis is known as cirrhosis.

**Useful For:**
- Evaluating hepatic fibrosis in chronic hepatitis C patients
- Diagnosing fibrosis in carriers of chronic hepatitis B virus
- Evaluating hepatic fibrosis in co-infected HIV carriers
- Providing access to new-generation non-interferon treatment for hepatitis
- Evaluating fibrosis in patients suffering from metabolic conditions (nonalcoholic fatty liver disease) and patients who consume excess alcohol

**Interpretation:**
FibroTest-ActiTest provides a score that assesses hepatic fibrosis (F0-F4) and a score that assesses hepatic inflammatory activity (A0-A3). Interpretation of the score is provided in the report. Individual results from the 6 component tests are also provided with institution-specific reference intervals. Fibrosis is reported relative to a scale ranging from F0-F4 (F0=no fibrosis, F1=minimal fibrosis, F2=moderate fibrosis, F3=advanced fibrosis, F4=severe fibrosis). Fibrosis scores may overlap (eg, F0/F1, F1/F2). Activity is reported relative to a scale ranging from A0-A3 (A0=no activity, A1=minimal activity, A2=significant activity, A3=severe activity). Activity scores may overlap (eg, A0/A1, A1/A2).

**Reference Values:**

<table>
<thead>
<tr>
<th>FibroTest Score</th>
<th>Stage</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.21*</td>
<td>F0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>0.21-0.27*</td>
<td>F0-F1</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>0.27-0.31*</td>
<td>F1</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.31-0.48*</td>
<td>F1-F2</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.48-0.58*</td>
<td>F2</td>
<td>Moderate fibrosis</td>
</tr>
<tr>
<td>0.58-0.72*</td>
<td>F3</td>
<td>Advanced fibrosis</td>
</tr>
<tr>
<td>0.72-0.74*</td>
<td>F3-F4</td>
<td>Advanced fibrosis</td>
</tr>
</tbody>
</table>
| 0.74-1.00       | F4    | Severe fibrosis (Cirrhosis) *Boundary values can apply to 2 stages based on rounding. For example, a FibroTest score of 0.305 will round up to 0.31 and be staged F1. A FibroTest score of 0.314 will round down to 0.31 and be staged F1-F2.

<table>
<thead>
<tr>
<th>ActiTest Score</th>
<th>Grade</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.17*</td>
<td>A0</td>
<td>No activity</td>
</tr>
</tbody>
</table>
immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FIGE
57916

Fig (Ficus carica) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0.10-0.34 
Equivocal/Borderline 0.35-0.69 Low Positive 0.70-3.49 Moderate Positive 3.50-17.49 High Positive 17.50-99.99 Very High Positive 99.99 Very High Positive

Reference Values:
<0.35 kU/L

FFAG4
57875

Filaria IgG4 Antibody, ELISA

Reference Values:
Reference Range: <1:50

Interpretive Criteria:

<1:50  Negative
1.50-3.00  Equivocal
>3.00  Positive

This assay detects Filaria IgG4 associated with infections caused by the major filarial parasites, including Dirofilaria immitis, Wuchereria bancrofti, Brugia malayi, and Onchocerca volvulus. Detection of IgG4 subclass antibody offers enhanced specificity without sacrifice of sensitivity. Chronic filarial infections manifesting as elephantiasis may not show a significant IgG4 response, and cannot be ruled out by this assay. Equivocal results may represent cross-reactive antibodies induced by infection with other nematodes.

FIL
9232

Filaria, Blood

Clinical Information: The filariae are parasitic nematodes (roundworms) that cause significant human morbidity in tropical regions worldwide. The macroscopic adults live in the human host and release microscopic offspring (microfilariae) into the blood or skin. The microfilariae of Wuchereria bancrofti, Brugia malayi, B timori, Loa loa, Mansonella perstans, and M ozzardi are found in the blood, while the microfilariae of Onchocerca volvulus and M streptocerca are found in the skin. If microfilariae are taken up by a biting insect vector (mosquitoes, blackflies, midges, and deer flies), they undergo further development in the insect and can then be transmitted to other humans. W bancrofti and the Brugia species cause a serious condition called lymphatic filariasis. The adults live in the lymphatics and cause inflammation and scarring of the lymph vessels. Over time, the lymphatic channels are obstructed and fluid cannot drain back to the heart, resulting in massive lymphedema (elephantiasis) of the affected limb or groin. W bancrofti is found in the tropics worldwide, while Brugia species are found in parts of Asia and Southeast Asia. Loa loa causes migratory subcutaneous angioedema referred to as "calabar swellings" as the adult worm migrates throughout the body. The adult occasionally migrates across the surface of the eye, giving it the moniker "the African eye worm." Loa loa is only
found in Africa. Finally, M perstans and M ozzardi cause a relatively mild form of filariasis. Patients are often asymptomatic. When present, symptoms include fever, angioedema, headache, myalgias, arthralgias, pruritus, and neurologic manifestations. M perstans is found in parts of Africa and South America, while M ozzardi is only found in Mexico and Central and South America. The microfilariae of these filarial worms can be seen on conventional thick and thin blood films, which allows for their definitive identification. However, microfilariae may be in low numbers and, therefore, use of concentration methods such as the Knott's technique improves the detection sensitivity. Some microfilariae are released into the blood at certain times of the day; W bancrofti and Brugia species are usually released between 10 p.m. and 2 a.m. (nocturnal periodicity), while L loa is released mostly from 10 a.m. and 2 p.m. (diurnal periodicity). It is therefore important to collect blood during these time periods for optimal detection sensitivity. Mansonella species microfilariae do not exhibit any periodicity and, therefore, a random blood draw is acceptable. Since the levels of parasitemia may fluctuate, multiple smears may be needed to detect the filarial worms. Blood should be obtained and examined every 8 to 12 hours for 2 to 3 days before excluding infection.

**Useful For:** Detection of microfilariae in peripheral blood

**Interpretation:** Positive results are provided with the genus and species of the microfilariae, if identifiable.

**Reference Values:**

- Negative
- If positive, organism is identified.

**Clinical References:** Centers for Disease Control and Prevention, Division of Parasitic Diseases and Malaria. DPDx, Diagnostic Procedures. 2013. Available at http://www.cdc.gov/dpdx/diagnosticProcedures/blood/specimencoll.html

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**Finch Feathers, IgE, Serum**

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

**Useful For:** Establishing the diagnosis of an allergy to finch feathers
- Defining the allergen responsible for eliciting signs and symptoms
- Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

- Class IgE kU/L

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

FANT 82698

Fire Ant, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to fire ant Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

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**Firebush (Kochia), IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to firebush (Kochia) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**First Trimester Maternal Screen, Serum**

**Clinical Information:** Multiple marker serum screening has become a standard tool used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects such as Down syndrome (trisomy 21) and trisomy 18 (Edward syndrome). Since early 2000s first-trimester screening has been established as an alternative option of equal or better performance when compared to second-trimester screening programs. The first-trimester screen is performed by measuring analytes human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) in maternal
serum that are produced by the fetus and the placenta. Additionally, the nuchal translucency (NT) measurement, a sonographic marker shown to be effective in screening fetuses for Down syndrome and trisomy 18, is included in the risk calculation. A mathematical model is used to calculate a risk estimate by combining serum concentrations to hCG and PAPP-A, NT measurement, and maternal demographic information. The laboratory establishes a specific cutoff for each condition, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered. Human Chorionic Gonadotropin (Total Beta-hCG) hCG is synthesized by placental cells starting very early in pregnancy and serves to maintain the corpus luteum and, hence, progesterone production during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with an increased risk for Down syndrome. Low levels of hCG are associated with an increased risk for trisomy 18. Pregnancy-Associated Plasma Protein A (PAPP-A) PAPP-A is a 187 kDA protein comprised of 4 subunits: 2 PAPP-A subunits and 2 pro-major basic protein (proMBP) subunits. PAPP-A is a metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4), dramatically reducing IGFBP-4 affinity for IGF1 and IGF2, thereby regulating the availability of these growth factors at the tissue level. PAPP-A is highly expressed in first-trimester trophoblasts, participating in regulation of fetal growth. Levels in maternal serum increase throughout pregnancy. Low PAPP-A levels before the 14th week of gestation are associated with an increased risk for Down syndrome and trisomy 18. Nuchal Translucency (NT) The NT measurement, an ultrasound marker, is obtained by measuring the fluid-filled space within the nuchal region (back of the neck) of the fetus. While fetal NT measurements obtained by ultrasonography increase in normal pregnancies with advancing gestational age, Down syndrome fetuses have larger NT measurements than gestational age-matched normal fetuses. Increased fetal NT measurements can therefore serve as an indicator of an increased risk for Down syndrome and trisomy 18.

Useful For: Prenatal screening for Down syndrome and trisomy 18

Interpretation: Screen-Negative: A screen-negative result indicates that the calculated risk is below the established cutoff of 1/230 for Down syndrome and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 18 or Down syndrome. Screen-negative results typically do not warrant further evaluation. Screen-Positive: When a Down syndrome risk cutoff of 1/230 is used for follow-up, the first trimester maternal screen has an overall detection rate of approximately 85% with a false-positive rate of 5%. In practice, both the detection rate and false-positive rate increase with age, thus detection and positive rates will vary depending on the age distribution of the screening population.

Reference Values:
DOWN SYNDROME
Calculated screen risks <1/230 are reported as screen negative.
Risks > or =1/230 are reported as screen positive.

TRISOMY 18
Calculated screen risks <1/100 are reported as screen negative.
Risks > or =1/100 are reported as screen positive. A numeric risk for trisomy 18 risk is provided with positive results on non-diabetic, non-twin pregnancies.
An interpretive report will be provided.

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

**FLEC**

**9243**

**Flecainide, Serum**

**Clinical Information:** Flecainide (Tambocor) is a Class I cardiac antiarrhythmic agent indicated for treatment of paroxysmal supraventricular dysrhythmia, paroxysmal atrial fibrillation/flutter, and life-threatening ventricular dysrhythmias. After oral administration, flecainide is nearly completely absorbed and peak concentrations are attained in approximately 3 hours. The half-life averages approximately 20 hours, but is widely variable (12 to 27 hours) and steady-state concentrations are typically achieved in approximately 5 days. Flecainide is eliminated from blood by hepatic metabolism, as well as renal clearance; significant changes in either organ system will cause impaired clearance. Common adverse effects include dizziness, visual disturbances, and dyspnea. Mild-to-moderate toxicity is associated with dizziness, visual disturbances, headache, nausea, fatigue, palpitations, and chest pain. Visual hallucinations and dysarthria may occur at toxic serum concentrations. Death can occur from hypotension, respiratory failure, and asystole.

**Useful For:** Optimizing dosage Assessing toxicity Monitoring compliance

**Interpretation:** Flecainide is most effective in premature ventricular contractions suppression at serum concentrations in the range of 0.2 to 1.0 mcg/mL. Serum concentrations above 1.0 mcg/mL are associated with a high rate of cardiac adverse experiences such as conduction defects or bradycardia.

**Reference Values:**
Trough Value
- 0.2-1.0 mcg/mL: Therapeutic concentration
- >1.0 mcg/mL: Toxic concentration

**Clinical References:**

**FLI1**

**70432**

**FLI-1 Immunostain, Technical Component Only**

**Clinical Information:** Friend leukemia integration 1 transcription factor (FLI1) is a member of the erythroblast transformation specific (ETS) family of transcription factors. It has anti-apoptotic activity and also interferes with nuclear hormone receptors. A chromosomal translocation between the FLI1 gene and EWS gene is found in most Ewing sarcomas. In normal tissues, nuclear staining is seen in endothelial cells, a subset of T cells, megakaryocytes and normal breast epithelium. FLI1 expression also occurs in endothelial-derived tumors, Ewing sarcoma, Merkel cell carcinoma, lung adenocarcinoma, melanoma, and erythroleukemia.

**Useful For:** Aiding in phenotyping endothelial-derived tumors, Ewing sarcoma, Merkel cell carcinoma, lung adenocarcinoma, melanoma, and erythroleukemia

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the
stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FLNDR** 57895

**Flounder (Bothidae/Pleuronectidae Fam) IgE**

**Interpretation:** Class IgE (kU/L)

<table>
<thead>
<tr>
<th>Comment</th>
<th>0 &lt;0.10</th>
<th>Negative</th>
<th>0/1 0.10</th>
<th>Åêå,¬ÔêΩ 0.34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivocal/Borderline</td>
<td>1 0.35</td>
<td>Åêå,¬ÔêΩ 0.69</td>
<td>Low Positive</td>
<td>2 0.70 Åêå,¬ÔêΩ 3.49 Moderate Positive</td>
</tr>
<tr>
<td></td>
<td>3 3.50</td>
<td>Åêå,¬ÔêΩ 17.49 High Positive</td>
<td>4 17.50 Åêå,¬ÔêΩ 49.99 Very High Positive</td>
<td>5 50.00 Åêå,¬ÔêΩ 99.99 Very High Positive</td>
</tr>
<tr>
<td></td>
<td>6 &gt;99.99 Very High Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reference Values:**

kU/L <0.35

**FLT** 19739

**FLT3 Mutation Analysis, Varies**

**Clinical Information:** The FMS-like tyrosine gene (FLT3) codes for a transmembrane receptor/signaling protein (FLT3) of the tyrosine kinase group. Binding of FLT3 ligand to the FLT3 receptor ultimately leads to production of proteins that cause cell growth and inhibit cell death through apoptosis. Recently, variants in FLT3 have been found in some hematopoietic neoplasms and are particularly common in adult acute myeloid leukemia (AML) with an overall incidence of approximately 20% to 30%. The highest genetic variant rates are seen in adult patients with AML and normal- or intermediate-risk cytogenetics, and patients with acute promyelocytic leukemia. The most common FLT3 variant consists of internal tandem duplication (ITD) of DNA sequences found in exons 14 or 15. In some subgroups of adults with AML, the presence of an FLT3 ITD variant has been found to be an adverse prognostic indicator. The second most common variant is a point alteration in the codon for an aspartate residue (D835) that resides in the activation loop of the FLT3 protein. D835 alterations have been identified in approximately 7% of AML cases but, at this time, it is not clear if the presence of this alteration has any prognostic significance. It is thought that both types of FLT3 variants lead to constitutive (always present, independent of internal or external stimuli) FLT3 activation. Identification of an FLT3 variant in AML is clinically useful, not only because of the prognostic information it provides, but also because FLT3-inhibitory drugs have shown promise as useful therapeutic agents.

**Useful For:** A prognostic indicator in some patients with acute myeloid leukemia. This test should not be used to monitor residual disease following treatment.

**Interpretation:** An interpretive report will be issued indicating whether the FLT3 internal tandem duplication (ITD), D835 alteration, or both were detected. Variant status will be indicated as positive or negative. If ITD positive, an allelic ratio will be reported.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:** 1. Levis M, Small D: FLT3: ITDoes matter in leukemia. Leukemia. 2003
Flunitrazepam Confirmation, Serum

**Reference Values:**

Units:  
- Flunitrazepam ng/mL
- 7-Aminoflunitrazepam ng/mL

Peak plasma Flunitrazepam concentrations in patients receiving chronic, recommended dosages: 10–20 ng/mL.

**Fluoride, Plasma**

**Clinical Information:** Fluoride induces bone formation by stimulating osteoblasts. Because fluorides increase bone density, they are used in dental preparations and as an antiosteoporotic agent. However, prolonged high exposure to fluoride produces changes in bone morphology consistent with osteomalacia, including prolonged mineralization lag time and increased osteoid thickness. The adverse skeletal effects of fluoride are associated with plasma fluoride greater than 4 mcmol/L. Chronic fluorosis may produce osteosclerosis, periostitis, calcification of ligaments and tendons, and crippling deformities. Prolonged exposure to the fluoride-containing antifungal agent voriconazole can produce high plasma fluoride concentrations and bone changes (periostitis). Several other medicines also contain fluoride are used for treating skin diseases (eg, flucytosine, an antifungal) and some cancers (eg, fluorouracil, an antimetabolite).

**Useful For:** Assessing accidental fluoride ingestion Monitoring patients receiving sodium fluoride for bone disease or patients receiving voriconazole therapy

**Interpretation:** Humans exposed to fluoride-treated water typically have plasma fluoride in the range of 1 to 4 mcmol/L. Those who are not drinking fluoride-treated water have plasma fluoride less than 1 mcmol/L. Plasma fluoride values greater than 4 mcmol/L indicate excessive exposure and are associated with periostitis.

**Reference Values:**

<4.1 mcmol/L


Fluoxetine, Serum

**Clinical Information:** Fluoxetine is a selective serotonin reuptake inhibitor approved for treatment of bulimia, obsessive-compulsive behavior, panic disorders, premenstrual dysphoria, and major depressive disorder, with a variety of off-label uses. Both fluoxetine and its major metabolite, norfluoxetine, are pharmacologically active and are reported together in this assay. Most individuals respond optimally
when combined serum concentrations for both parent and metabolite are in the therapeutic range (120-500 ng/mL) at steady state. Due to the long half-lives of parent and metabolite (1-6 days), it may take several weeks for patients to reach steady-state concentrations. Fluoxetine is a potent inhibitor of the metabolic enzyme cytochrome P450 (CYP) 2D6, with lesser inhibitory effects on CYP2C19 and CYP3A. Therapy with fluoxetine is, therefore, subject to numerous drug interactions, which is compounded by wide interindividual variability in fluoxetine pharmacokinetics. Measurement of the drug is useful for managing comedications, dose or formulation changes, and in assessing compliance. Side effects are milder for fluoxetine than for older antidepressants such as the tricyclics. The most common side effects of fluoxetine therapy include nausea, nervousness, anxiety, insomnia, and drowsiness. Anticholinergic and cardiovascular side effects are markedly reduced compared to tricyclic antidepressants. Fatalities from fluoxetine overdose are extremely rare.

**Useful For:** Monitoring serum concentration of fluoxetine during therapy Evaluating potential toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to fluoxetine when combined serum levels of fluoxetine and norfluoxetine are between 120 and 500 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. A toxic range has not been well established.

**Reference Values:**
Fluoxetine + Norfluoxetine: 120-500 ng/mL

**Clinical References:**

**Fluphenazine (Prolixin), Serum**

**Reference Values:**
Reference Range: 1.0 - 10 ng/mL

**Flurazepam (Dalmane) and Desalkylflurazepam**

**Reference Values:**
Flurazepam:
Reference Range: 0 - 30 ng/mL

Desalkylflurazepam:
Reference Range: 30 - 150 ng/mL

Flurazepam + Desalkylflurazepam:
Reference Range: 30 - 180 ng/mL
Fluticasone 17-Beta-Carboxylic Acid, Random, Urine

Clinical Information: Inhaled corticosteroids are the single most effective therapy for adult patients with asthma. Even low doses of inhaled corticosteroids have been shown to reduce mortality related to asthma. The September 2007 issue of Pediatrics reported that "Verification of (asthma) treatment adherence by objective measures remains necessary."(1) In this pediatric asthma adherence study, the 104 asthmatic children and their parents grossly overestimated their medication adherence. Over 1 of 3 responses reported full compliance to medications when no medications had been taken. Over 46% of individuals exaggerated their adherence by at least 25%. The authors concluded that "Under the best of conditions in this study, accuracy of self-report was insufficient to provide a stand-alone measure of adherence."(1,2) Fluticasone propionate (FP) is an inhaled corticosteroid with anti-inflammatory and immunosuppressive properties commonly used for the treatment of asthma, airway inflammation, and allergic rhinitis. FP is typically well tolerated and has a low risk for adverse systemic effects when utilized at recommended therapeutic doses. However, noncompliance with recommended FP therapy may result in poorly controlled asthma or misinterpretation of the patient's therapeutic responsiveness. Patients with excessive exposure to FP may present with clinical features of Cushing syndrome, but with evidence of hypothalamus-pituitary-adrenal axis suppression, including suppressed cortisol levels. Conversely, a patient not administering the drug as recommended may have their therapeutic responsiveness interpreted, in error by the patient or clinician, as steroid-resistance. FP has low oral bioavailability and high hepatic first-pass metabolism, which results in low plasma FP concentrations; any systemic levels are believed to occur through adsorption from the lungs. Native FP absorbed by the gastrointestinal tract (<1% total FP) is rapidly metabolized by cytochrome P450 isoform 3A4 to yield fluticasone 17-beta-carboxylic acid, its primary metabolic product.(3) Fluticasone 17-beta-carboxylic acid is pharmacologically inactive and has increased water solubility such that it is excreted in urine. Accordingly, fluticasone 17-beta-carboxylic acid is detected in urine in individuals recently exposed to inhaled FP therapy. Fluticasone 17-beta-carboxylic acid may be detected in urine as early as 16 to 24 hours following a patient's first administration of low dose (220 mcg) FP therapy. The window of detection for fluticasone 17-beta-carboxylic acid is 6 days following cessation of FP therapy.

Useful For: Assessing compliance (recent exposure) to fluticasone propionate therapy An aid in the evaluation of secondary adrenal insufficiency

Interpretation: Elevated fluticasone 17-beta-carboxylic acid indicates recent exposure to fluticasone propionate (FP). Fluticasone 17-beta carboxylic acid concentration <10 pg/mL indicates that the patient may not have administered inhaled FP therapy within the preceding 6 days. Validated concerns about suboptimal patient adherence to asthma controller medications should lead to patient and provider interactions to address potential compliance issues.

Reference Values:
Negative
Cutoff concentration: 10 pg/mL

Values for normal patients not taking fluticasone propionate should be less than the cutoff concentration (detection limit).

Reference Values:
Units: ng/mL

Expected fluvoxamine concentrations on recommended daily dosage regimens:
50-900 ng/mL

**IAPC 113345**

**FNA Immediate Adequacy (Bill Only)**

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

**IAAPC 113346**

**FNA Immediate Adequacy Add'l (Bill Only)**

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

**PGXQP 610057**

**Focused Pharmacogenomics Panel, Varies**


**Useful For:** Preemptive or reactive genotyping of patients for pharmacogenomic purposes Providing an assessment for genes with strong drug-gene associations

**Interpretation:** An interpretive report will be provided, which focuses on only drugs and genes with published pharmacogenomic practice guidance by the Clinical Pharmacogenetics Implementation Consortium, other professional organizations or where strong FDA guidance has been issued in drug labels. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**FOL 9198**

### Folate, Serum

**Clinical Information:** The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate. Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characteristically associated with macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions. Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

**Useful For:** Investigation of suspected folate deficiency

**Interpretation:** Serum folate is a relatively nonspecific test. Low serum folate levels may be seen in the absence of deficiency, and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results below 4 mcg/L are suggestive of folate deficiency. The cutoff is based on consensus and was derived from the US NHANES III data. Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Serum folate measurement is preferred over RBC folate measurement due to considerable analytic variability (coefficient of variation) of assays. Both results give the same interpretation (internal Mayo study), therefore, RBC folate quantitation is not recommended. Additional serum testing with homocysteine and methylmalonic acid (MMA) determinations may help distinguish between vitamin B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, the analytic variability of both serum and RBC folate assays is considerable. Homocysteine and MMA levels are alternate determinants of folate deficiency. See Vitamin B12 Deficiency Evaluation in Special Instructions.

**Reference Values:**

- > 4.0 mcg/L
- < 4.0 mcg/L suggests folate deficiency


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**FSHB 70433**

### Follicle Stimulating Hormone, Beta Subunit (Beta FSH)

**Immunostain, Technical Component Only**

**Clinical Information:** Follicle stimulating hormone (FSH) stimulates maturation of ovarian follicles...
and estrogen secretion in females. Sparse population of cells stain positively in normal pituitary gland (approximately 10% of cells). This population of gonadotrophs also produces luteinizing hormone. Immunohistochemical detection of beta FSH (bFSH) may be useful in the classification of pituitary adenomas.

**Useful For:** Classification of pituitary adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FSH 602753**

**Follicle-Stimulating Hormone (FSH), Serum**

**Clinical Information:** Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, follicle-stimulating hormone (FSH), and LH from the anterior pituitary. The menstrual cycle is divided by a midcycle surge of both FSH and LH into a follicular phase and a luteal phase. FSH appears to control gametogenesis in both males and females.

**Useful For:** An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

**Interpretation:** In both males and females, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. FSH and LH are generally elevated in: -Primary gonadal failure -Complete testicular feminization syndrome -Precocious puberty (either idiopathic or secondary to a central nervous system lesion) -Menopause (postmenopausal FSH levels are generally >40 IU/L) -Primary ovarian hypofunction in females -Primary hypogonadism in males Normal or decreased FSH in: -Polycystic ovary disease in females FSH and LH are both decreased in failure of the pituitary or hypothalamus.

**Reference Values:**

**Males**
- <12 months: < or =3.3 IU/L
- > or =12 months-< or =5 years: < or =1.9 IU/L
- >5 years-< or =10 years: < or =2.3 IU/L
- >10 years-< or =15 years: 0.6-6.9 IU/L
- >15 years-< or =18 years: 0.7-9.6 IU/L
- >18 years: 1.2-15.8 IU/L

**TANNER STAGES**
- Stage I: <1.5 IU/L
- Stage II: <3.0 IU/L
Stage III: 0.4-6.2 IU/L  
Stage IV: 0.6-5.1 IU/L  
Stage V: 0.8-7.2 IU/L  

*Puberty onset occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females  
<12 months: 1.2-12.5 IU/L  
> or =12 months-< or =10 years: 0.5-6.0 IU/L  
>10 years-< or =15 years: 0.9-8.9 IU/L  
>15 years-< or =18 years: 0.7-9.6 IU/L  

Premenopausal:  
Follicular: 2.9-14.6 IU/L  
Midcycle: 4.7-23.2 IU/L  
Luteal: 1.4-8.9 IU/L  
Postmenopausal: 16.0-157.0 IU/L  

**TANNER STAGES**  
Stage I: 0.6-4.1 IU/L  
Stage II: 0.3-5.8 IU/L  
Stage III: 0.1-7.2 IU/L  
Stage IV: 0.3-7.0 IU/L  
Stage V: 0.4-8.6 IU/L  

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

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

**Clinical References:**  

**Food Panel #2, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing a diagnosis of an allergy to cabbage, paprika, spinach, and tomato. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3 3.50-17.4</td>
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<tr>
<td>4 17.5-49.9</td>
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<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 ≥100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**FFPG4 Food Panel IgG4 (532)**

**Reference Values:**
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

**FFPII Food Panel II IgG**

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

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

**Useful For:** Establishing a diagnosis of an allergy to codfish, cow's milk, egg white, peanut, soybean, and wheat. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens:
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>0.35-0.69</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
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<td>5</td>
<td>50.0-99.9</td>
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<tr>
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<td>&gt; or =100</td>
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</table>

Reference values apply to all ages.


**Food-Fruit Panel, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to apple, banana, peach, and pear Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more
allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of
allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or
greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the
allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum
varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus
MR, eds. Henry’s Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier;
2017:1057-1070

**Food-Nut Panel # 1, Serum**

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more
allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of
allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Food-Nut Panel # 2, Serum

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

Useful For: Establishing a diagnosis of an allergy to cashew, pecan, pistachio, and walnut

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tbody>
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<td></td>
<td>Negative</td>
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</table>

Food-Seafood Panel, Serum

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

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

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>0</td>
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<td>1</td>
<td>0.35-0.69</td>
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Reference values apply to all ages.
Formaldehyde, IgE, Serum

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

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

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

Reference Values:

<table>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Formic Acid, Serum

**Interpretation:** Formic acid is also a metabolite of methanol, formaldehyde, and methyl formate among others. Values may vary depending on environmental and occupational exposures, diet, nutritional condition, and pregnancy status.

**Reference Values:**
- Reporting limit determined each analysis
- Units: mcg/mL
- Normal plasma formic acid range is 1 - 9 mcg/mL
  (in pregnant women, 0.5 - 44 mcg/mL).

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Formic Acid, Urine

**Reference Values:**
- Reporting limit determined each analysis

Creatinine (mg/L)
- U.S. Population (10th - 90th percentiles, median)
  - All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
  - Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
  - Females: 273 - 2170 mg/L, median 994 (n=11,635)

Formic Acid (mcg/mL)
- Synonym(s): Formate
- In a study of 70 non-exposed individuals, the median level of formic acid in urine was 13.6 mcg/mL (range 1.0-95 mcg/mL). Formic acid is also a metabolite of methanol, formaldehyde, and methyl formate among others. Values may vary depending on environmental and occupational exposures, diet, nutritional condition, and pregnancy status.

Formic Acid (Creatinine Corrected) (mg/g Creat)
- Synonym(s): Formate
- In a study of 70 non-exposed individuals, the median level of formic acid in urine was 14 mg/g creatinine with the 95th

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FosB, Immunostain, Technical Component Only

**Clinical Information:** FosB is a member of the Fos transcription factor family and a component of the activator protein-1 (AP-1) protein complex. Expressed in the nucleus, FosB is useful in the diagnosis of pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma (PHE) and may be helpful to distinguish it from its histologic mimics. FosB is also found in a subset of epithelioid hemangiomas.

**Useful For:** Diagnosing pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma (PHE) and epithelioid hemangiomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Sugita S, Hirano H,
FOXL2 Mutation Analysis, Tumor

Clinical Information: Granulosa cell tumor (GCT) represents approximately 5% to 10% of all ovarian malignancies and is the most common type of malignant ovarian sex-cord stromal tumor. The majority of patients with GCT (95%) are adults and 5% are juveniles. The histopathological diagnosis of GCT is challenging. Forkhead box L2 (FOXL2) gene is involved in ovarian development and function. The FOXL2 gene point mutation 402C->G in exon 1 (C134W) was reported in the majority of adult GCT (>90%), 5% to 10% of thecomas (tumors closely related to GCT) and less than 10% of juvenile GCT cases, but not in other ovarian tumors. Detection of FOXL2 mutation aids in the clinical diagnosis of adult GCT. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations in the FOXL2 gene known to be associated with adult GCT. The results of this test can be useful for supporting a diagnosis of adult GCT.

Useful For: Assisting in the clinical diagnosis of adult granulosa cell tumor (GCT) by assessing gene targets with in the FOXL2 gene. This test is not useful for hematological malignancies.

Interpretation: An interpretative report will be provided.

Reference Values: An interpretative report will be provided.

Clinical References:

FOXP1 Immunostain, Technical Component Only

Clinical Information: Forkhead box protein 1 (FOXP1) is a member of the forkhead box family of transcription factors that have a variety of functions in different cell and tissue types. Gene expression profiling and immunophenotypic studies showed that FOXP1 is expressed in normal activated B cells and overexpressed in a subset of diffuse large B-cell lymphomas (DLBCL) with a predominantly nongerminatal center phenotype.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:
2. Hoeller S, Schneider A, Haralambieva E, Dirnhofer S,

**FOXP3 Immunostain, Technical Component Only**

**Clinical Information:** Forkhead box P3 (FOXP3) is a transcription factor implicated in T-cell regulation, activation, and differentiation. FOXP3 has been shown to be a master control gene for the development and function of CD4+/CD25+ regulatory T cells. In normal lymphoid tissues, a T-cell subset in interfollicular areas shows nuclear staining. FOXP3 is a specific marker for adult T-cell leukemia/lymphoma (ATLL).

**Useful For:** Classification of leukemias and lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Foxtail Millet, IgE, Serum**

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

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

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

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*


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**Fragile X Syndrome, Molecular Analysis, Varies**

**Clinical Information:** Fragile X syndrome is an X-linked disorder with variable expression in males and females. In greater than 99% of affected individuals, it is caused by an expansion of the CGG trinucleotide repeat in the 5'UTR (untranslated region) of the FMR1 gene, located on the X chromosome. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 5 to 44. These normal alleles are passed from generation to generation with the number of repeats remaining constant. Small expansions, called premutations, range from 55 to 200 CGG repeats. Individuals with a premutation do not exhibit features of fragile X syndrome but are at risk for other FMR1-related disorders such as fragile X tremor/ataxia syndrome (FXTAS) and premature ovarian insufficiency (POI). Transmission of a premutation by a male to his daughter usually results in little or no change in the FMR1 repeat number. Transmission of a premutation by a female to her son or daughter usually results in further expansion, either to a larger premutation or a full mutation. The risk for a female with a premutation to have a child affected with fragile X syndrome by expansion to a full mutation increases with the number of CGG repeats in the premutation. Full mutations are typically greater than 200 repeats long and are associated with abnormal methylation of a region adjacent to the FMR1 gene. This is thought to interfere with normal FMR1 gene expression, resulting in fragile X syndrome. There are multiple clinical phenotypes associated with expansion (premutations and full mutations) in the FMR1 gene. Fragile X Syndrome: Approximately 1 in 4000 individuals (male and female) are affected with fragile X syndrome. Most affected males exhibit moderate mental retardation with affected females having milder, if any, cognitive deficiency. Neuropsychiatric diagnoses, such as autism spectrum and anxiety disorders, are common. Characteristic physical features include a long face with prominent jaw, protruding ears, connective tissue abnormalities, and large testicles in postpubertal males. Fragile X Tremor/Ataxia Syndrome (FXTAS): FXTAS is a neurodegenerative disorder that is clinically distinct from fragile X syndrome. Both males and females with a premutation are at risk for FXTAS. However, the disorder is much less common and milder in clinical presentation than fragile X syndrome, and shows a later age of onset in females. Clinical hallmarks of the disorder include intention tremor, gait ataxia, dementia, and neuropsychiatric symptoms. The risk for FXTAS increases as the number of CGG repeats increases, and the majority of individuals with FXTAS have CGG repeat expansions of 70 or more. Penetrance of clinical symptoms is associated with increasing age, with the majority of affected males showing symptoms between age 70 and 90. Premature Ovarian Insufficiency (POI): Females with a premutation are at risk for increased follicular stimulating hormone (FSH) levels, early menopause, and POI. Penetrance and early onset of female reproductive symptoms correlates with increasing size of the CGG repeat and reaches its highest penetrance at approximately 80 to 90 repeats. Of note, penetrance actually remains stable or may even
decrease at approximately 100 repeats. There is no risk for increased penetrance of the POI phenotype due to maternal or paternal inheritance of the expanded CGG repeat.

**Useful For:** Confirmation of a diagnosis of fragile X syndrome, fragile X tremor/ataxia syndrome, or premature ovarian insufficiency caused by expansions in the FMR1 gene. Determination of carrier status for individuals with a family history of fragile X syndrome or X-linked intellectual disability. Prenatal diagnosis of fragile X syndrome when there is a documented FMR1 expansion in the family.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
- Normal alleles: 5-44 CGG repeats
- Intermediate (grey zone) alleles: 45-54 CGG repeats
- Premutation alleles: 55-200 CGG repeats
- Full mutation alleles: >200 CGG repeats

An interpretive report will be provided.

**Methylation status:**
- Unmethylated: < or =20%
- Partially methylated: 21-69%
- Fully methylated: > or =70%

**Clinical References:**

**FUFXS**

**Fragile X, Follow up Analysis**

**Reference Values:**
This is not an orderable test.

This follow-up test is added by the laboratory dependent upon on the result of the PCR analysis (FXS / Fragile X Syndrome, Molecular Analysis).

**TULG**

**Francisella tularensis Antibody, IgG, ELISA, Serum**

**Clinical Information:** Francisella tularensis is a small, intracellular, coccobacillary Gram negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks and deerflies. F tularensis is found throughout North America and parts of Asia, and similar to Brucella species is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3 to 5 day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule which ultimately ulcerates following which the bacterium enters the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease, however it lacks the ulceration and more frequently causes septicemia. Other, less frequent clinical manifestations include ocuologlandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, pneumonic or typhoidal tularemia. Diagnostic testing options for F tularensis are currently unavailable.
primarily include culture and serology. Physicians suspecting tularemia should collect appropriate specimens (e.g., skin lesion biopsy, lymph node aspirates, etc.) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularemia. Serologic testing may be used to support a diagnosis of current or recent tularemia in patients who are IgM positive, or seroconvert to IgM, or IgG positive in paired sera collected 2 to 3 weeks apart.

**Useful For:** Aiding in the diagnosis of tularemia caused by Francisella tularensis using IgG antibody testing. This assay should not be used as a test of cure as it is not quantitative and patients may remain seropositive for months to years following resolution of disease.

**Interpretation:**

<table>
<thead>
<tr>
<th>IgM Result</th>
<th>IgG Result</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| Negative   | Negative   | No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 2 to 3 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgM and IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

**Reference Values:**

Only orderable as part of a profile. For more information see Francisella tularensis Antibody, IgM and IgG, ELISA, Serum.

- Negative
- Reference values apply to all ages.

**Clinical References:**


**TULAB 605950**

**Francisella tularensis Antibody, IgM and IgG, ELISA, Serum**

**Clinical Information:**

Francisella tularensis is a small, intracellular, coccobacillary Gram-negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks, and deerflies. F tularensis is found throughout North America and parts of Asia, and similar to Brucella species is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (e.g., tick, deerfly). Following a 3 to 5 day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule that ultimately ulcerates allowing the bacterium to enter the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease, however it lacks the ulceration and more frequently causes septicemia. Other, less frequent clinical manifestations include oculoglandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, pneumatic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Physicians suspecting tularemia should collect appropriate specimens (e.g., skin lesion biopsy, lymph node aspirates, etc) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that
appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularensis. Serologic testing may be used to support a diagnosis of current or recent tularensis in patients who are IgM positive, who seroconvert to IgM, or who are IgG positive in paired sera collected 2 to 3 weeks apart.

**Useful For:** Aiding in the diagnosis of tularemia caused by Francisella tularensis This test should not be used as a test of cure as it is not quantitative and patients may remain seropositive for months to years following resolution of disease.

**Interpretation:** IgM result IgG result Interpretation Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 2 to 3 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

**Francisella tularensis Antibody, IgM and IgG, Technical Interpretation, Serum**

**Clinical Information:** Francisella tularensis is a small, intracellular, coccobacillary Gram negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks and deerflies. F tularensis is found throughout North America and parts of Asia, and similar to Brucella species is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3 to 5 day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule which ultimately ulcerates following which the bacterium enters the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease, however it lacks the ulceration and more frequently causes septicemia. Other, less frequent clinical manifestations include oculoglandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, pneumonic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Physicians suspecting tularemia should collect appropriate specimens (eg, skin lesion biopsy, lymph node aspirates, etc.) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularensis. Serologic testing may be used to support a diagnosis of current or recent tularensis in patients who are IgM positive, or seroconvert to IgM, or IgG positive in paired sera.
Useful For: Interpretation for the aid in the diagnosis of tularemia caused by Francisella tularensis. This assay should not be used as a test of cure as it is not quantitative and patients may remain seropositive for months to years following resolution of disease.

Interpretation: IgM Result IgG Result Interpretation
Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 2 to 3 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

Reference Values:
Only orderable as part of a profile. For more information see Francisella tularensis Antibody, IgM and IgG, ELISA, Serum.


Francisella tularensis Antibody, IgM, ELISA, Serum

Clinical Information: Francisella tularensis is a small, intracellular, cocccobacillary Gram negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks and deerflies. F tularensis is found throughout North America and parts of Asia, and similar to Brucella species is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3 to 5 day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule which ultimately ulcerates following which the bacterium enters the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease, however it lacks the ulceration and more frequently causes septicemia. Other, less frequent clinical manifestations include ocuologlandular (Parinaud syndrome), ooropharyngeal and gastrointestinal disease, pneumatic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Physicians suspecting tularemia should collect appropriate specimens (eg, skin lesion biopsy, lymph node aspirates, etc.) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularemia. Serologic testing may be used to support a diagnosis of current or recent tularemia in patients who are IgM positive, or seroconvert to IgM, or IgG positive in paired sera collected 2 to 3 weeks apart.

Useful For: Aiding in the diagnosis of tularemia caused by Francisella tularensis using IgM antibody testing. This assay should not be used as a test of cure as it is not quantitative and patients may remain seropositive for months to years following resolution of disease.
**Interpretation:**

IgM Result IgG Result Interpretation

Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 2 to 3 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

**Reference Values:**

Only orderable as part of a profile. For more information see Francisella tularensis Antibody, IgM and IgG, ELISA, Serum.

Negative
Reference values apply to all ages.

**Clinical References:**


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**NEFA**

**606892**

**Free Fatty Acids, Total, Serum**

**Clinical Information:** Elevated serum concentrations of nonesterified fatty acids (NEFA) are associated with cardiovascular disease, metabolic syndrome, obesity, and type 2 diabetes mellitus. NEFA are causally linked with insulin resistance and inflammation of vascular endothelium.

**Useful For:** Evaluation of metabolic status of patients with endocrinopathies Monitoring of control of diabetes mellitus. Monitoring the effects of therapeutic diet/exercise lifestyle changes

**Interpretation:** Abnormally high levels of free fatty acids are associated with uncontrolled diabetes mellitus and with conditions that involve excessive release of a lipoactive hormone such as epinephrine, norepinephrine, glucagon, thyrotropin, and adrenocorticotropic.

**Reference Values:**

> or =18 years: 0.00-0.72 mmol/L
Reference values have not been established for patients who are <18 years of age.

**Clinical References:**


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**FRTUP**

**62583**

**Free Thyroxine Index (FTI), Serum**

**Clinical Information:** The determination of the total thyroxine (T4) concentration is of importance in laboratory diagnostics for differentiating between euthyroid, hyperthyroid, and hypothyroid conditions. As the major fraction of the total T4 is bound to transport proteins (thyroxine-binding globulin: TBG,
prealbumin, and albumin), the determination of total T4 only provides correct information when the thyroxine-binding capacity (TBC) in serum is normal. The free thyroid hormones are in equilibrium with the hormones bound to the carrier proteins. The TBC or T-uptake assay provides a measure of the available thyroxine-binding sites. Determination of the free thyroxine index (FTI) from the quotient of total T4 and thyroxine-binding index (ie, result of the T-uptake determination) takes into account changes in the thyroid hormone carrier proteins and the thyroxine level. While total T4 is a relatively reliable indicator of T4 levels in the presence of normal binding proteins, it is not a reliable indicator when binding proteins are abnormal. For example, increases in thyroxine-binding proteins may cause increased total T4 levels despite normal free T4 levels and normal thyroid function. Results are changed by drugs or physical conditions that alter the patient's TBG levels, or drugs that compete with endogenous T4 and T3 for protein-binding sites. Direct measurement of free thyroxine (FRT4 / T4 [Thyroxine], Free, Serum by immunoassay) has replaced the FTI test in most clinical situations.

**Useful For:** Estimating the amount of circulating free thyroxine (free thyroxine index) using the total thyroxine and thyroid binding capacity (T-uptake)

**Interpretation:** The free thyroxine index (FTI) is determined by the following calculation: FTI = Thyroxine (T4)/Thyroid Binding Capacity The FTI is a normalized determination that remains relatively constant in healthy individuals and compensates for abnormal levels of binding proteins. Hyperthyroidism causes increased FTI and hypothyroidism causes decreased values.

**Reference Values:**

**THYROXINE BINDING CAPACITY** (units are in Thyroxine Binding Index: TBI):

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19 years</td>
<td>0.8-1.2 TBI</td>
</tr>
<tr>
<td>&gt; or =20 years</td>
<td>0.8-1.3 TBI</td>
</tr>
</tbody>
</table>

**T4 TOTAL (T4):**

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 days</td>
<td>5.0-18.5 mcg/dL</td>
</tr>
<tr>
<td>6 days-2 months</td>
<td>5.4-17.0 mcg/dL</td>
</tr>
<tr>
<td>3-11 months</td>
<td>5.7-16.0 mcg/dL</td>
</tr>
<tr>
<td>1-5 years</td>
<td>6.0-14.7 mcg/dL</td>
</tr>
<tr>
<td>6-10 years</td>
<td>6.0-13.8 mcg/dL</td>
</tr>
<tr>
<td>11-19 years</td>
<td>5.9-13.2 mcg/dL</td>
</tr>
<tr>
<td>&gt; or =20 years</td>
<td>4.5-11.7 mcg/dL</td>
</tr>
</tbody>
</table>

**FREE THYROXINE INDEX:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 days</td>
<td>5.1-20.8 mcg/dL</td>
</tr>
<tr>
<td>6 days-2 months</td>
<td>5.5-18.0 mcg/dL</td>
</tr>
<tr>
<td>3-11 months</td>
<td>5.7-16.8 mcg/dL</td>
</tr>
<tr>
<td>1-5 years</td>
<td>5.9-15.0 mcg/dL</td>
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<tr>
<td>6-10 years</td>
<td>6.0-13.9 mcg/dL</td>
</tr>
<tr>
<td>11-19 years</td>
<td>5.9-13.2 mcg/dL</td>
</tr>
<tr>
<td>&gt; or =20 years</td>
<td>4.8-12.7 mcg/dL</td>
</tr>
</tbody>
</table>

For SI unit Reference Values, see [www.mayocliniclabs.com/order-tests/si-unit-conversion.html](http://www.mayocliniclabs.com/order-tests/si-unit-conversion.html)

Free-Living Amebae, Molecular Detection, PCR, Varies

Clinical Information: Several free-living amebae can infect the central nervous system (CNS) and cause devastating, usually fatal, disease. The route of entry and clinical course of infection varies with the type of ameba involved. Naegleria fowleri typically causes rapidly progressive primary amebic meningoencephalitis (PAM) in previously healthy children or adults. Infection is acquired during contact with contaminated water, including swimming and diving in warm stagnant freshwater lakes and by nasal irrigation with nonsterile water. During contact, the amebae enter the nasal sinuses and travel along the olfactory nerve through the cribriform plate of the skull and into the CNS. PAM is almost uniformly fatal within several days of exposure. Because of the rarity of the infection and difficulty in initial detection, about 75% of diagnoses are made after the death of the patient. In contrast, Acanthamoeba species and Balamuthia mandrillaris usually cause a subacute CNS illness, usually in adults who are immunocompromised, called granulomatous amebic encephalitis (GAE). The presentation of GAE can mimic a brain abscess, aseptic or chronic meningitis, or CNS malignancy. The amebae may enter the nasal sinuses like N fowleri or can disseminate to the CNS from the lungs or a primary skin lesion. These amebae are usually identified by microscopic examination of cerebrospinal fluid or brain tissue and agar culture. Culture is more sensitive than microscopy alone but takes up to 7 days to produce a positive result. Also, B mandrillaris will not grow in routine culture. Real-time polymerase chain reaction assays offers a rapid and sensitive alternative to microscopy and culture.

Useful For: Aids in the diagnosis of primary amebic meningoencephalitis and granulomatous amebic encephalitis in spinal fluid and tissue in conjunction with clinical findings This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of free-living ameba DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of primary amebic meningoencephalitis and granulomatous amebic encephalitis.

Reference Values:
Negative

Clinical References:

Friedreich Ataxia Repeat Expansion Analysis - Unknown Mutation

Reference Values:
A final report will be attached in MayoAccess.

Friedreich Ataxia, Frataxin, Quantitative, Blood

Clinical Information: Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 individuals in the white population. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Cardiac involvement occurs with the development of myocardial fibrosis due to mitochondrial proliferation and loss of contractile proteins. It tends to be correlated with the clinical neurologic age of onset and the GAA triplet repeat length, but not the duration of disease or the severity of neurologic symptoms. Although most individuals begin experiencing initial symptoms between 10 and 15 years of age, atypical late-onset forms with initial symptoms presenting after age 25 do occur. FA is caused by variants in the FXN gene encoding a mitochondrial protein, frataxin. Variants in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 98% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of FXN. The remaining 2% of FA patients have the trinucleotide expansion on 1 allele and a point alteration or deletion on the second allele.
Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1700 repeats, though the majority of individuals with FA have repeats ranging from 600 to 1200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. Unfortunately, testing for the triplet repeat expansion will miss those patients with point alterations or deletions. Moreover, a molecular-based analysis is not able to effectively monitor treatment. In contrast, a protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA.

**Useful For:** Diagnosing individuals with Friedreich ataxia in whole blood specimens Monitoring frataxin levels in patients with Friedreich ataxia This test is not useful for carrier detection.

**Interpretation:** Normal results (> or = 19 ng/mL for pediatric and > or = 21 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

**Reference Values:**
Pediatric (<18 years) normal frataxin: > or = 19 ng/mL Adults (> or =18 years) normal frataxin: > or = 21 ng/mL.

**Clinical References:**

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**Friedreich Ataxia, Frataxin, Quantitative, Blood Spot**

**Clinical Information:** Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 individuals in the white population. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Cardiac involvement occurs with the development of myocardial fibrosis due to mitochondrial proliferation and loss of contractile proteins. It tends to be correlated with the clinical neurologic age of onset and the GAA triplet repeat length, but not the duration of disease or the severity of neurologic symptoms. Although most individuals begin experiencing initial symptoms between 10 and 15 years of age, atypical late-onset forms with initial symptoms presenting after age 25 do occur. FA is caused by variants in the FXN gene encoding a mitochondrial protein, frataxin. Variants in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 98% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of FXN. The remaining 2% of FA patients have the trinucleotide expansion on 1 allele and a point alteration or deletion on the second allele. Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1700 repeats, though the majority of individuals with FA have repeats ranging from 600 to 1200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. Unfortunately, testing for the triplet repeat expansion will miss those patients with point alterations or deletions. Moreover, a molecular-based analysis is not able to effectively monitor treatment. In contrast, a protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA.

**Useful For:** Diagnosing individuals with Friedreich ataxia in blood spot specimens Monitoring frataxin levels in patients with Friedreich ataxia This test is not useful for carrier detection.

**Interpretation:** Normal results (> or = 15 ng/mL for pediatric and > or = 21 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

**Reference Values:**
Pediatric (<18 years) normal frataxin: > or = 15 ng/mL
Adults (> or =18 years) normal frataxin: > or =21 ng/mL

**Clinical References:**

**PCIFS**
Frozen Section, 1st Block (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**PCAFS**
Frozen Section, Additional Blocks (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**FRUCT**
Fructosamine, Serum
Clinical Information: Fructosamine is a general term, which applies to any glycated protein. It is formed by the nonenzymatic reaction of glucose with the a- and e-amino groups of proteins to form intermediate compounds called aldimines. These aldimines may dissociate or undergo an Amadori rearrangement to form stable ketoamines called fructosamines. This nonenzymatic glycation of specific proteins in vivo is proportional to the prevailing glucose concentration during the lifetime of the protein. Therefore, glycated protein measurement in the diabetic patient is felt to be a better monitor of long-term glycemic control than individual or sporadic glucose determinations. The best known of these proteins is glycated hemoglobin which is often measured as hemoglobin A1c, and reflects glycemic control over the past 6 to 8 weeks. In recognition of the need for a measurement that reflects intermediate-term glycemic control and was easily automated, a nonspecific test, termed fructosamine, was developed. Since albumin is the most abundant serum protein, it accounts for 80% of the glycated serum proteins, and thus, a high proportion of the fructosamine. Although a large portion of the color generated in the reaction is contributed by glycated albumin, the method will measure all proteins, each with a different half-life and different levels of glycation.

Useful For: Assessing intermediate-term glycemic control

Interpretation: In general, fructosamine reflects glycemic control in diabetic patients over the previous 2 to 3 weeks. High values indicate poor control.

Reference Values:
200-285 mcmol/L

Clinical References:

**FROS2**
Fructose, Qualitative, Semen

Current as of June 14, 2021 12:13 pm CDT
800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Clinical Information:** Fructose is produced in the male reproductive tract by the seminal vesicles and is released into the semen during ejaculation. Fructose is the energy source for sperm motility.

**Useful For:** Establishing the origin of azoospermia in patients with azoospermia and low volume ejaculates

**Interpretation:** A positive (indicated by color change) fructose is considered normal. A semen specimen that contains no sperm (azoospermia) and is fructose negative may indicate an absence of the seminal vesicles, absence of the vas deferens in the area of the seminal vesicles, or an obstruction at the level of the seminal vesicles.

**Reference Values:**
Positive

**Clinical References:**

**FFPG**

**Fruit Panel IgG**

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

**GFDZ**

**FTCD Gene, Full Gene Analysis, Varies**

**Clinical Information:** Glutamate formiminotransferase deficiency is an autosomal recessive inborn error of folate and histidine metabolism caused by a deficiency of the enzyme, glutamate formiminotransferase-cyclodeaminase, which is encoded at the FTCD loci on chromosome 21q22.3. Glutamate formiminotransferase deficiency presents as a clinical spectrum that ranges from asymptomatic to severe. Individuals with the severe form of disease are reported to have mental and physical retardation and anemia, whereas the mild form is associated with a lesser degree of developmental delay. Of note, the association of the enzyme deficiency with mental retardation has been disputed in the literature. An elevated amount of urine formiminoglutamate (FIGLU) is a cardinal sign of glutamate formiminotransferase deficiency for both the severe and mild clinical phenotypes. However, higher levels of urine FIGLU are observed in patients with milder forms of the disease and these levels occur in the absence of histidine loading; whereas the presence of FIGLU in the urine is typically only observed in severe cases after L-histidine administration. In addition, the severe form of disease is associated with elevated serum folate levels, whereas the milder form of disease is not. As there are discrepancies in FIGLU and serum folate levels among affected individuals, confirmation of suspected cases of glutamate formiminotransferase deficiency may require a liver biopsy for enzymology or the identification of 2 disease-causing mutations in the FTCD gene. Identification of 2 FTCD mutations establishes a molecular diagnosis of glutamate formiminotransferase deficiency, and rules out other diseases associated with high levels of urine FIGLU, such as folate or methylcobalamin deficiencies. Evaluation of the FTCD gene by molecular genetic testing is recommended as a second-tier test subsequent to a positive newborn screen or biochemical test.

**Useful For:** Second-tier test for confirming glutamate formiminotransferase deficiency (indicated by biochemical testing or newborn screening) Ruling out other diseases associated with high levels of urine formiminoglutamate Carrier screening in cases where there is a family history of glutamate formiminotransferase deficiency but disease-causing mutations have not been identified in an affected individual
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**Fumarate Hydratase Immunostain, Technical Component Only**

**Clinical Information:** A ubiquitously expressed mitochondrial enzyme fumarate hydratase (FH) catalyzes the reversible hydration of fumaric acid to yield I-malic acid during the Krebs cycle. Germline alterations in the FH gene cause a predisposition to renal defects like hereditary leiomyomatosis and renal cell carcinoma (HLRCC). While morphologic features are characteristic enough that they can be suspected, FH deficiency or germline DNA testing are necessary for its diagnosis. HLRCC can be associated with multiple cutaneous leiomyomas, uterine leiomyomas, and an aggressive variant of renal cell carcinoma (RCC) that occurs frequently in young patients.

**Useful For:** Identifying fumarate hydratase-deficient neoplasms Supporting the diagnosis of an atypical smooth muscle tumor over leiomyosarcoma

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
NA


**Fungal Culture, Blood**

**Clinical Information:** Due to the high mortality rate from fungemia, the expeditious detection and identification of fungi from the patient's blood can have great diagnostic prognostic importance. Risk factors for fungemia include, but are not limited to, extremes of age, immunosuppression, and those individuals with burns or indwelling intravascular devices.
Useful For: Diagnosis and treatment of the etiologic agents of fungemia Select patient population that presents with signs and symptoms of sepsis, especially fever of unknown origin

Interpretation: Positive cultures of yeast and filamentous fungi are reported with the organism identification. Positive cultures are usually an indication of infection and are reported as soon as detected. Correlation of culture results and the clinical situation is required for optimal patient management. A final negative report is issued after 30 days of incubation.

Reference Values:
Negative
If positive, notification is made as soon as the positive culture is detected or identified.


FDERM
87283

Fungal Culture, Dermal

Clinical Information: Fungal infections of keratinized tissues (hair, skin, nails) can be caused by dermatophytic fungi belonging to the genera Epidermophyton, Microsporum, and Trichophyton. Opportunistic superficial infections resembling dermatophytoses may be caused by yeasts or by unrelated filamentous fungi that are normally saprobes or plant pathogens. Dermatophytes are usually unable to penetrate deeper tissues. Infection may range from mild to severe.

Useful For: Recovery and identification of dermatophyte fungi from hair, skin, and nail infected specimens

Interpretation: Positive cultures are reported with organism identification. Negative reports are issued after 30 days incubation.

Reference Values:
Negative
If positive, fungus or yeast will be identified.


FGEN
84389

Fungal Culture, Routine

Clinical Information: Many fungi in the environment cause disease in immunocompromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (eg, persons with AIDS, patients receiving chemotherapy or transplant rejection therapy) has increased. Isolation and identification of the infecting fungus in the clinical laboratory can help guide patient care.

Useful For: Diagnosing fungal infections from specimens other than blood, skin, hair, nails, and vagina (separate tests are available for these specimen sites)

Interpretation: Positive cultures of yeast and filamentous fungi are reported with the organism identification. The clinician must determine whether or not the presence of an organism is significant. A final negative report is issued after 24 days of incubation.

Reference Values:
Negative
If positive, fungus will be identified.

FVAG

Fungal Culture, Vaginal

Clinical Information: Candidal vulvovaginitis is believed to be the most frequent or second most frequent vaginal infection. Depending on the geographical area, its prevalence in women is estimated to be in the range of 5% to 20%. Besides Candida albicans, Candida glabrata, and Candida tropicalis are the most frequently isolated Candida species both from vulvo-vaginitis patients and from healthy carriers.

Useful For: Monitoring therapy for vulvovaginitis Managing chronic recurring disease Determining the etiology of infectious vaginitis when other tests have been uninformative

Interpretation: Meaningful diagnosis of vaginal candidiasis requires that 1) yeast are demonstrable in the affected area and 2) clinical symptoms and signs are consistent with the disease. Since in up to 20% of healthy women, yeast cells are part of the normal vaginal flora, the presence of Candida on culture may be meaningless or misleading unless other clinical factors are considered.

Reference Values:
Negative

If positive, yeast will be identified.


FUNA

Fungal Ident Panel A (Bill Only)

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

FUNB

Fungal Ident Panel B (Bill Only)

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

D2F

Fungal Sequencing Identification

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

FS

Fungal Smear, Varies

Clinical Information: Many fungi in the environment cause disease in severely compromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (persons with AIDS, patients receiving chemotherapy or transplant...
rejection therapy, etc) has increased. Few fungal diseases can be diagnosed clinically; most are diagnosed by isolating and identifying the infecting fungus in the clinical laboratory.

**Useful For:** Detection of fungi in clinical specimens

**Interpretation:** Positive slides are reported as one or more of the following: yeast or hyphae present, organism resembling Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, or Malassezia furfur.

**Reference Values:**
Negative


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**Fungitell, BAL**

**Clinical Information:** The Fungitell Beta-1,3-D Glucan assay detects (1,3)-β-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3)-β-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3)-β-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3)-β-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in BAL have been determined by Viracor-Eurofins; there are no established criteria for the interpretation of Fungitell results from BAL fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2003) 123:1302-1307).

**Reference Values:**
A reference range for specimens other than serum has not been established.

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**Fungitell, bronch wash**

**Clinical Information:** The Fungitell Beta-1,3-D Glucan assay detects (1,3)-β-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3)-β-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3)-β-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3)-β-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in bronchial wash have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from bronchial wash fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2013) 123:1302-1307).

**Reference Values:**
A reference range for specimens other than serum has not been established.
**Fungitell, CSF**

**Clinical Information:** The Fungitell Beta-D Glucan assay is indicated for the presumptive diagnosis of invasive fungal disease through detection of elevated levels of (1,3)-Beta-D-glucan in serum. Normal human serum contains low levels of (1,3)-Beta-D-glucan, typically 10 to 40 pg/mL, presumably from commensal yeasts present in the alimentary canal and gastrointestinal tract. However, (1,3)-Beta-D-glucan is sloughed from the cell walls during the life cycle of most pathogenic fungi. Thus, monitoring serum for evidence of elevated and rising levels of (1,3)-Beta-D-glucan provides a convenient surrogate marker for invasive fungal disease. The Fungitell Beta-D Glucan assay detects (1,3)-Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccioidoides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3)-Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3)-Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3)-Beta-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in CSF have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from CSF fluid. Research studies have evaluated the use of the Fungitell assay in CSF during a fungal meningitis outbreak (J. Clin. Microbiol. 2013, 51(4):1285-1287).

**Reference Values:**
A reference range for specimens other than serum has not been established.

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**Furosemide (Lasix)**

**Reference Values:**
Expected serum furosemide concentration in patients on usual daily dosages: Up to 5.0 ug/mL

Toxic: greater than 50.0 ug/mL

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**FUS Immunostain, Technical Component Only**

**Clinical Information:** Fused in sarcoma (FUS), also known as translated in liposarcoma (TLS), protein is a multifunctional DNA- and RNA-binding protein. Studies have shown the cause of familial amyotrophic lateral sclerosis (ALS) to be an alteration in the gene encoding the FUS protein. FUS has been linked to other neurodegenerative diseases including frontotemporal lobar dementia (FTLD) and neuronal intermediate filament inclusion disease (NIFID).

**Useful For:** Identification of frontotemporal lobar dementia (FTLD)

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Fusarium moniliforme, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Fusarium moniliforme Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Fusarium oxysporum/vasinfectum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Å¬ë¢â¬â€œ 0.69 Low Positive 2 0.70 Å¬ë¢â¬â€œ 3.49 Moderate Positive 3 3.50 Å¬ë¢â¬â€œ 17.49 Positive 4 17.50 Å¬ë¢â¬â€œ 49.99 Strong Positive 5 50.00 Å¬ë¢â¬â€œ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** ≤0.35 kU/L
**Gabapentin, Serum**

**Clinical Information:** Gabapentin is an antiepileptic drug that is effective in treating seizures, neuropathies, and a variety of neurological and psychological maladies. Although designed as a gamma amino butyric acid (GABA) analogue, gabapentin does not bind to GABA receptors, nor does it affect the neuronal uptake or degradation of GABA. In fact, the precise mechanism by which it exerts its analgesic and anticonvulsant effects is unknown. After oral administration and absorption, gabapentin circulates essentially unbound to serum proteins. In addition, gabapentin does not undergo hepatic metabolism, unlike most other antiepileptic drugs, and is eliminated almost entirely by renal excretion with a clearance that approximates the glomerular filtration rate. The elimination half-life is 5 to 7 hours in patients with normal renal function. Since gabapentin does not bind to serum proteins, it does not exhibit pharmacokinetic variability and interactions with other highly protein-bound medications (e.g., phenytoin). In addition, the lack of hepatic metabolism eliminates the interactions with other hepatically cleared medications, which can induce/inhibit hepatic drug metabolizing enzyme systems (cytochrome P450s). Therefore, gabapentin serum concentrations are not changed following the addition or discontinuation of other common anticonvulsants (i.e., phenobarbital, phenytoin, carbamazepine, or valproic acid), nor are their serum concentration altered upon the addition or discontinuation of gabapentin. In general, adverse effects with gabapentin are infrequent and usually resolve with continued treatment. The most common side effects include somnolence, dizziness, ataxia, and fatigue. Experience to date indicated that gabapentin is safe and relatively nontoxic.

**Useful For:** Monitoring serum gabapentin concentrations Assessing compliance Adjusting dosage in patients

**Interpretation:** Therapeutic ranges are based on specimens collected immediately before the next dose (i.e., trough). Most epileptic patients show response to the drug when the trough concentration is in the range of 2-20 mcg/mL. Therapeutic drug monitoring may be useful due to inter-individual variation in pharmacokinetics and dose-dependent bioavailability; specimens for measurements should be collected before the morning dose since the short half-life may affect the interpretation of the concentration.

**Reference Values:**

- 2.0-20.0 mcg/mL
- Toxic Range: > or =25.0 mcg/mL

**Clinical References:**

**Gabapentin, Urine**

**Reference Values:**

- Reference Range: Not Established
- Units: ug/mL

**Gadolinium, 24 Hour, Urine**

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. Patients with reduced renal
function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

**Useful For:** Assessing chronic exposure and monitoring effectiveness of dialysis in a 24-hour urine collection

**Interpretation:** Elevated urine gadolinium results from a specimen collected more than 96 hours after administration of a gadolinium-based contrast agent confirms past exposure, or continued exposure through anthropogenic sources and prolonged elimination of gadolinium. Gadolinium also has been shown to be present in some municipal water sources, which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to gadolinium-based contrast agents (GBCA). Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis (NSF).

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17 years</td>
<td>not established</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>&lt;1.1 mcg/24 hours</td>
</tr>
</tbody>
</table>

**Clinical References:**


**Gadolinium, Dermal, Tissue**

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.
Useful For: Evaluation of dermal tissue for gadolinium

Interpretation: Elevated gadolinium (>0.5 mcg/g) observed in dermal tissue specimens collected more than 96 hours after administration of gadolinium-based contrast agents indicates some gadolinium deposition. In a small internal study (n=13), patients with histologically confirmed nephrogenic systemic fibrosis (NSF), a history of renal failure, and exposure to gadolinium-based contrast agents (GBCA) had gadolinium concentrations in the range of 6.3 to 348.7 mcg/g in affected tissues. However, unaffected tissues from gadolinium-exposed subjects showed gadolinium concentrations in the range of 0.6 to 68.2 mcg/g. A detectable gadolinium concentration in tissue suggests recent or past exposure to GBCA.

Reference Values:
<0.5 mcg/g


GDS 89299

Gadolinium, Serum

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

Useful For: Aiding in documenting past exposure to gadolinium-based contrast agents in serum specimens

Interpretation: Elevated gadolinium observed in serum specimens drawn more than 96 hours after administration of gadolinium-containing contrast media is not typical of most patients with normal renal function, and may indicate prolonged elimination of gadolinium and exposure to anthropogenic sources.

Reference Values:
<0.5 ng/mL

Gadolinium/Creatinine Ratio, Random, Urine

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents; GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCA. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

**Useful For:** Assessing chronic exposure and monitoring effectiveness of dialysis in a random urine collection

**Interpretation:** Elevated urine gadolinium results from a specimen collected more than 96 hours after administration of a gadolinium-based contrast agent confirms past exposure, or continued exposure through anthropogenic sources and prolonged elimination of gadolinium. Gadolinium also has been shown to be present in some municipal water sources, which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to gadolinium-based contrast agents (GBCA). Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis (NSF).

**Reference Values:**
0-17 years: not established
> or =18 years: <0.8 mcg/g creatinine

**Clinical References:**
**GATOL 62440**

**Galactitol, Quantitative, Urine**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylytransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, cognitive and intellectual disabilities, and death. Galactosemia is treated with a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, abnormalities of motor function, and females are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000. Galactose levels may be continuously elevated in individuals affected with galactosemia even with a galactose-restricted diet regimen due to an endogenous production of galactose. The reduction of galactose to galactitol is an alternate pathway of galactose disposition when galactose metabolism is impaired. The excretion of abnormal quantities of galactitol in the urine of patients is characteristic of this disorder, and patients may have abnormal levels of galactitol even with dietary compliance. Daily consumption of galactose may cause urine levels to rise thus providing information on effectiveness of or compliance with treatment, but unlike erythrocyte galactose-1-phosphate (GAL1P) and plasma galactose, urine galactitol levels usually do not provide insight into acute and transient effects of galactose intake.

**Useful For:** Monitoring effectiveness of treatment in patients with galactosemia Establishing a baseline level prior to initiating treatment for galactosemia

**Interpretation:** The concentration of galactitol is provided along with reference ranges for patients with galactosemia and normal controls.

**Reference Values:**

- 0-11 months: <109 mmol/mol creatinine
- 1-3 years: <52 mmol/mol creatinine
- 4-17 years: <16 mmol/mol creatinine
- > or =18 years: <13 mmol/mol creatinine


**GALCR 606280**

**Galactocerebrosidase Reflex, Leukocytes**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of the enzyme, galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide and lactosylsphingosine) causing severe demyelination throughout the brain. Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A (SAP-A) have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by 2 years of age. Some individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe...
GALCW

606270

Galactocerebrosidase, Leukocytes

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of the enzyme, galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide and lactosylsphingosine causing severe demyelination throughout the brain. Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. Some individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early
Identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Reduced or absent galactocerebrosidase in leukocytes can indicate a diagnosis of Krabbe disease, however a number of alterations in the GALC gene have been identified that result in reduced galactocerebrosidase activity in vitro, but do not cause disease. The biomarker, psychosine (see PSY / Psychosine, Blood Spot) has been shown to be elevated in patients with active Krabbe disease. Molecular sequencing of the GALC gene (see KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR, Varies) is necessary for differentiating alterations from disease-causing variants in affected patients and for carrier detection in family members.

**Useful For:** Diagnosis of Krabbe disease Follow-up testing for evaluation of an abnormal newborn screening result for Krabbe disease This test is not intended for carrier detection.

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

**Reference Values:**
> or = 0.30 nmol/hour/mg protein

An interpretative report will be provided.

**Clinical References:**

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**Galactokinase, Blood**

**Clinical Information:** Galactokinase (GALK) deficiency, is a very rare autosomal recessive disorder in the first step of galactose metabolism. Prevalence is unknown but estimated to be approximately 1 in 50,000-1 in 100,000 live births, with a higher frequency in the Romani population. Individuals with GALK deficiency have a milder clinical presentation than that seen in patients with classic galactosemia, galactose-1-phosphate uridyltransferase (GALT) deficiency. The major clinical manifestation is bilateral juvenile cataracts. GALK deficiency is treated with a galactose-restricted diet. Early treatment may prevent or reverse the formation of cataracts. In GALK deficiency, erythrocyte galactose-1-phosphate levels are generally normal and plasma or urine galactose levels are generally elevated. The diagnosis is established by demonstrating deficient GALK enzyme activity in erythrocytes. Testing for GALK deficiency should be performed when there is a suspicion of galactosemia, either based upon the patient's clinical presentation or laboratory studies and GALT deficiency has been excluded. Specimens sent for GALT analysis may be used for GALK testing if the original specimen was received in the laboratory within the stability parameters listed in Specimen Stability Information. GALK deficiency is caused by variants in the GALK1 gene. Gene analysis is available from some commercial laboratories. Call 800-533-1710 for recommendations or contact information for laboratories that offer this testing. See Galactosemia Testing Algorithm in Special Instructions.

**Useful For:** Diagnosis of galactokinase deficiency Evaluation of children with unexplained bilateral congenital or juvenile onset cataracts
Interpretation: An interpretive report will be provided. Deficient galactokinase (GALK) enzyme activity in erythrocytes is diagnostic for galactokinase deficiency. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Reference Values:
> or =0.7 nmol/h/mg of hemoglobin


Galactose, Quantitative, Plasma

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Screening for galactosemia

Interpretation: Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate, Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn, and, in rare cases, galactose intolerance. If results are outside the normal range and galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. See Ordering Guidance for test ordering guidance.

Reference Values:
< or =7 days: <5.4 mg/dL
8-14 days: <3.6 mg/dL
> or =15 days: <2.0 mg/dL

Galactosemia, Quantitative, Urine

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia; however, these are only general patterns and further confirmatory testing would be required to make a diagnosis. Deficiency Galactose (Plasma/Urine) Gal-1-P (Blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Screening test for galactosemia using urine specimens

Interpretation: Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate, Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn and, in rare cases, galactose intolerance. If galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis.

Reference Values:
<30 mg/dL


Galactose-1-Phosphate Uridyltransferase Biochemical Phenotyping, Erythrocytes

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute
symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Duarte-variant galactosemia (compound heterozygosity for the Duarte variant, N314D and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure and were often treated with a low galactose diet during infancy. More recently, the outcomes data suggest a lack of evidence for developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second variant, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. In general, molecular genetic analysis with a panel of common variants (GAL14/ Galactosemia Gene Analysis (14-Mutation Panel)) is typically performed to determine the specific genotype. If the enzymatic and molecular results are incongruent, biochemical phenotyping and/or molecular sequence analysis may be beneficial to help clarify results to determine a treatment strategy and recurrence risks. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Determining the biochemical phenotype for galactosemia when enzymatic and molecular results are incongruent

Interpretation: An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Reference Values:
An interpretative report will be provided.

Clinical References:

GALT Galactose-1-Phosphate Uridyltransferase, Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal-1-P (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia
(compound heterozygosity for the Duarte variant, N314D and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure and were often treated with a low galactose diet during infancy. More recently, the outcomes data suggest a lack of evidence for developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second variant, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT variants may be performed. If 1 or both disease-causing variants are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private variations. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Useful For:** Diagnosis of galactose-1-phosphate uridylyltransferase deficiency, the most common cause of galactosemia Confirmation of abnormal state newborn screening results

**Interpretation:** An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Reference Values:**
> or = 24.5 nmol/h/mg of hemoglobin

**Clinical References:**

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**GAL1P**

**Galactose-1-Phosphate, Erythrocytes**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency. The quantitative measurement of Gal-1-P Â is useful for monitoring compliance with dietary therapy for either deficiency. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. The concentration of Gal-1-P in erythrocytes is the most sensitive index of dietary control. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia due to GALT deficiency is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency
galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared with intermediate epimerase deficiency galactosemia, which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and renal dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of renal and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, females with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6700 in African American infants to 1 in 70,000 in infants of European ancestry. See Galactosemia Testing Algorithm in Special Instructions.

**Useful For:** Monitoring dietary therapy of patients with galactosemia due to deficiency of galactose-1-phosphate uridyltransferase or uridine diphosphate galactose-4-epimerase

**Interpretation:** The concentration of galactose-1-phosphate (Gal-1-P) is provided along with reference values for patients with galactosemia and normal controls. The recommended Gal-1-P goal for patients with galactosemia is less than or equal to 4.9 mg/dL. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Reference Values:**
Reference interval (normal range): < or = 0.9 mg/dL
Therapeutic range: < or = 4.9 mg/dL

**Clinical References:**

**Galactose-Alpha-1,3-Galactose (Alpha-Gal) Mammalian Meat Allergy Profile, Serum**

**Clinical Information:** Immunoglobulin E antibodies to galactose-alpha-1,3-galactose (alpha-gal), a carbohydrate commonly expressed on non-primate mammalian proteins, are capable of eliciting allergic reactions. Sensitization may occur through tick bites or exposure to the drug cetuximab. In the United States, individuals bitten by Amblyomma americanum, also known as the Lone Star tick, may develop IgE antibodies to alpha-gal, although sensitization to alpha-gal through other tick species has also been implicated.(1) The Lone Star tick was historically localized to the southern and southeastern United States but has now expanded its range into the central Midwest and northwards along the eastern seaboard. It is thought to be responsible for most cases of alpha-gal sensitization in the United States. The tick species that appears to be responsible for these responses in France is Ixodes ricinus, while in Australia it is Ixodes holocyclus.(2,3,4) Signs and symptoms of an alpha-gal allergic reaction are often delayed compared with other food allergies. Upon exposure of sensitized subjects to non-primate mammalian meat (e.g., beef, pork, venison) or meat-derived product such as gelatin, a delayed allergic response may ensue, often 3 to 6 hours after ingestion. Symptoms can include urticaria, angioedema, difficulty breathing, abdominal pain, vomiting, and even anaphylactic shock. Individuals who have antibodies produced against alpha-gal following a tick bite or previous exposure to the drug cetuximab may experience anaphylaxis when given cetuximab. Cetuximab is a monoclonal antibody, which contains an alpha-gal epitope on the antigen binding fragment (Fab fragment) of the monoclonal
drug. Unlike the delayed onset anaphylaxis associated with red meat consumption, individuals with IgE antibody response to alpha-gal can experience immediate onset anaphylaxis upon intravenous cetuximab administration. Although most sensitizations to alpha-gal occur later in life, children who develop IgE antibodies to alpha-gal may also experience anaphylaxis and urticaria 3 to 6 hours after eating mammalian meat. Unlike their adult counterparts, who frequently present with anaphylaxis, the majority of children with this syndrome present with urticaria. Alpha-gal can also be found in mammalian milk, including both cow and goat milk. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

**Useful For:** As an aid in diagnosis of an IgE mediated hypersensitivity allergy to non-primate mammalian red meat or meat-derived products, such as beef, pork, venison, and meat-derived products such as gelatin via allergen profile testing. This test is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists. This test is not useful for patients in whom the medical management does not depend upon identification of allergen specificity.

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
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<tr>
<td>0/1</td>
<td>0.10-0.34</td>
<td>Borderline/equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Concentrations > or =0.70 kU/L (Class 2 and above) will flag as abnormally high.

For BEEF, PORK, LAMB, MILK:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kUa/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Clinical References:**
ALGAL

609737

**Galactose-Alpha-1,3-Galactose (Alpha-Gal), IgE, Serum**

**Clinical Information:** Immunoglobulin E antibodies to galactose-alpha-1,3-galactose (alpha-gal), a carbohydrate commonly expressed on non-primate mammalian proteins, are capable of eliciting allergic reactions. Sensitization may occur through tick bites or exposure to the drug cetuximab. In the United States, individuals bitten by Amblyomma americanum, also known as the Lone Star tick, may develop IgE antibodies to alpha-gal, although sensitization to alpha-gal through other tick species has also been implicated. (1) The Lone Star tick was historically localized to the southern and southeastern United States but has now expanded its range into the central Midwest and northwards along the eastern seaboard. It is thought to be responsible for most cases of alpha-gal sensitization in the United States. The tick species that appears to be responsible for these responses in France is Ixodes ricinus, while in Australia it is Ixodes holocyclus. (2, 3, 4) Signs and symptoms of an alpha-gal allergic reaction are often delayed compared with other food allergies. Upon exposure of sensitized subjects to non-primate mammalian meat (e.g., beef, pork, venison) or meat-derived product such as gelatin, a delayed allergic response may ensue, often 3 to 6 hours after ingestion. Symptoms can include urticaria, angioedema, difficulty breathing, abdominal pain, vomiting, and even anaphylactic shock. Individuals who have antibodies produced against alpha-gal following a tick bite or previous exposure to the drug cetuximab may experience anaphylaxis when given cetuximab. Cetuximab is a monoclonal antibody, which contains an alpha-gal epitope on the antigen binding fragment (Fab fragment) of the monoclonal drug. Unlike the delayed onset anaphylaxis associated with red meat consumption, individuals with IgE antibody response to alpha-gal can experience immediate onset anaphylaxis upon intravenous cetuximab administration. Although most sensitizations to alpha-gal occur later in life, children who develop IgE antibodies to alpha-gal may also experience anaphylaxis and urticaria 3 to 6 hours after eating mammalian meat. Unlike their adult counterparts, who frequently present with anaphylaxis, the majority of children with this syndrome present with urticaria. Alpha-gal can also be found in mammalian milk, including both cow and goat milk. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

**Useful For:** As an aid in diagnosis of an IgE mediated hypersensitivity allergy to non-primate mammalian red meat or meat-derived products such as beef, pork, venison, and meat-derived products (e.g., gelatin) This test is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists. This test is not useful for patients in whom the medical management does not depend upon identification of allergen specificity.

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>
0/1 0.10-0.34 Borderline/equivocal
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Concentrations > or =0.70 Ku/L (Class 2 and above) will flag as abnormally high Reference values apply to all ages.


**GAL14 55071**

Galactosemia Gene Analysis, 14-Mutation Panel, Varies

Clinical Information: Classical galactosemia is an autosomal recessive disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, mental retardation, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte mutation, N314D and -119_-116delGTCA in cis [on the same chromosome], and a classic mutation in trans [on the opposite chromosome]) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are also often treated with a low-galactose diet during infancy. The Los Angeles (LA) variant, which consists of N314D without the presence of -119_-116delGTCA, is associated with normal levels of GALT enzyme activity. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by
targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutations. The GALT gene maps to 9p13. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic mutation. This mutation accounts for 60% to 70% of classical galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classical galactosemia. The 5 kb deletion is common in individuals of Ashkenazi Jewish descent. The Duarte mutation (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the mutations detected by this method (ie, D98N, S135L, T138M, M142K, F171S, Y209C, and Q344K) are all uncommon, but known to be recurrent in the general population. These mutations, in addition to the LA variant, are included in GAL14 / Galactosemia Gene Analysis (14-Mutation Panel) and in GCT / Galactosemia Reflex, Blood. See Galactosemia Testing Algorithm in Special Instructions for additional information. Refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Clinic Laboratories Communiqué 2005 May;30(5) for more information regarding diagnostic strategy.

Useful For: Second-tier test for confirming a diagnosis of galactosemia (indicated by enzymatic testing or newborn screening) Carrier testing family members of an affected individual of known genotype (has mutations included in the panel) Resolution of Duarte variant and Los Angeles (LA) variant genotypes

Interpretation: An interpretative report will be provided. Results should be interpreted in the context of biochemical results.

Reference Values: An interpretive report will be provided.


Galactosemia Reflex, Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal-1-P is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia (compound heterozygosity for the Duarte variant, N314D, and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure so were often treated with a low galactose diet during infancy. More recently however, the outcomes data suggest a lack of evidence for
developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second mutation, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT variants may be performed. If 1 or both disease-causing alterations are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private variants. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Useful For:** Preferred test for diagnosis, carrier detection, and determination of genotype of galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia
Differentiating Duarte variant galactosemia from classic galactosemia Confirming results of newborn screening programs

**Interpretation:** The laboratory provides an interpretation of the results, including galactose-1-phosphate uridyltransferase enzyme activity and genotype, if necessary. This interpretation provides an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional testing. Any specimen where enzyme activity is less than 24.5 nmol/h/mg of hemoglobin will be analyzed for the presence of 14 alterations associated with classic galactosemia, as well as the 2 variants (Duarte and Los Angeles). See Galactosemia Testing Algorithm in Special Instructions for testing algorithm and additional information. The GALT gene maps to chromosome 9p13. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic alteration. This alteration accounts for 60% to 70% of classical galactosemia alleles. The S135L allele is the most frequently observed in African Americans and accounts for approximately 50% of the variant alleles in this population. The K285N allele is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P allele is observed in 5% to 7% of classical galactosemia. The 5-kb deletion is common in individuals of Ashkenazi Jewish descent. The Duarte variant (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the variants detected by this method (ie, D98N, S135L, T138M, M142K, F171S, Y209C, and Q344K) are all uncommon but known to be recurrent in the general population. A high proportion (20%) of patients with classic galactosemia have a private alteration. Since our assay does not investigate for the presence of private variants, when GG, DG, or NG genotype is predicted by enzymatic studies and the current panel does not identify a variation, molecular sequencing may be indicated.

**Reference Values:**
> or = 24.5 nmol/h/mg of hemoglobin


**Galactosemia, GALT Gene, Full Gene Analysis, Varies**

**Clinical Information:** Classic galactosemia is an autosomal recessive disorder of galactose metabolism caused by variants in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, mental retardation, and death. Galactosemia is treated by a
galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D and a classic variant) is generally associated with higher levels of GALT activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are often treated with a low galactose diet during infancy. The LA variant, consisting of N314D and a second change, L218L, is associated with higher levels of GALT activity than the Duarte variant alone. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT activity. If enzyme activity levels are indicative of carrier or affected status, molecular testing for common GALT variants may be performed. If 1 or both disease-causing variants are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private variants. The GALT gene maps to 9p13 and more than 180 variants have been identified. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R variant, which accounts for 60% to 70% of classic galactosemia alleles. The S135L variant is the most frequently observed variant in the African American population and accounts for approximately 50% of the altered alleles in this population. The K285N variant is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P variant is observed in 5% to 7% of classic galactosemia. The Duarte variant (N314D) is found in 5% of the general United States population. The above variants, plus the LA variant, are included in GCT / Galactosemia Reflex, Blood, which is the preferred test for the diagnosis of galactosemia or for follow-up to positive newborn screening results. These variants are also included in GAL14 / Galactosemia Gene Analysis (14-Variant Panel). Varies. Full sequencing of the GALT gene can be useful for the identification of variants when 1 or no variants are found with these tests in an individual with demonstrated GALT activity deficiency. Full sequencing of the GALT gene identifies over 95% of the sequence variants in the coding region and splice junctions. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Useful For:** Identifying variants in individuals who test negative for the common variants and who have a biochemical diagnosis of galactosemia or galactose-1-phosphate uridyltransferase activity levels indicative of carrier status

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

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


**GAL1**

**606832**

**GALAD Score, Serum**

**Clinical Information:** Biomarkers of hepatocellular carcinoma (HCC) include alpha fetoprotein
(AFP), third electrophoretic form of lentil lectin-reactive AFP (AFP-L3), and des-carboxy-prothrombin (DCP). The GALAD model combines these three biomarkers with the patient’s gender and age to estimate the probability of HCC in patients with chronic liver disease based on the following equation

$$Z = -10.08 + 0.09 \times \text{age} + 1.67 \times \text{sex} + 2.34 \log(10) (\text{AFP}) + 0.04 \times \text{AFP-L3} + 1.33 \times \log(10) (\text{DCP}),$$

where sex = 1 for males, 0 for females. The probability estimate of HCC is calculated as follow

$$\text{Pr(HCC)} = \frac{\exp(Z)}{1 + \exp[Z]}.$$  

The GALAD model has been demonstrated to have higher diagnostic accuracy for the detection of HCC when compared to the use AFP, AFP-L3, and DCP markers alone or in combination. The performance of the GALAD score has also been reported to be superior to ultrasound for HCC detection.

**Useful For:** Calculation of the GALAD model score for hepatocellular carcinoma development in patients with chronic liver disease

**Interpretation:** The probability of the presence of hepatocellular carcinoma (HCC) is estimated from the GALAD model score. Higher GALAD model scores correlate with increased risk of HCC. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve of the GALAD score was 0.95 for all HCC detection, and 0.92 for the detection of early stage HCC. Additionally, the AUC of the GALAD score (0.95) was higher than that of ultrasound alone for all HCC detection (AUC of 0.82, P <0.01). The sensitivity and specificity performance characteristics of the GALAD score for HCC will be influenced by the selected GALAD score cut-off. For example at an optimal AUC cutoff of -0.76, the GALAD score had 91% sensitivity and 85% specificity for HCC detection. At a more specific GALAD score cutoff of 0.88, the observed sensitivity was 80% for HCC detection with an observed specificity of 97%. The GALAD model was developed and validated in patient cohorts with a prevalence of HCC ranging from 35% to 49%. The performance of the model may be altered in populations with different HCC prevalence. In addition, the clinical performance of the GALAD score varies by etiology of HCC and therefore may be different in different regions of the world.

**Reference Values:**

Only orderable as part of a profile. For more information see HCCGS / Hepatocellular Carcinoma Risk Panel with GALAD Score, Serum

Not applicable

**Clinical References:**


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**Galectin-3 Immunostain, Technical Component Only**

**Clinical Information:** Galectin-3 is a member of the beta-galactoside binding lectin family and is involved in cellular adhesion. It is expressed by normal macrophages, neutrophils, and mast cells. It is not expressed in normal or benign thyroid glands but may be expressed in thyroid carcinoma.

**Useful For:** Distinguishing normal and benign thyroid gland from thyroid carcinoma

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation.
or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Galectin-3, Serum

Clinical Information: Heart failure is a complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are readmitted within the forthcoming year, incurring costly treatments and therapies. The development and progression of heart failure is a clinically silent process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically, heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury and/or stress. Galectin-3 is a biomarker that appears to be actively involved in both the inflammatory and some fibrotic pathways. Galectin-3 is a carbohydrate-binding lectin whose expression is associated with inflammatory cells including macrophages, neutrophils, and mast cells. Galectin-3 has been linked to cardiovascular physiological processes including myofibroblast proliferation, tissue repair, and cardiac remodeling in the setting of heart failure. Concentrations of galectin-3 have been used to predict adverse remodeling after a variety of cardiac insults.

Useful For: Aiding in the prognosis for patients diagnosed with heart failure Risk-stratification of heart failure patients An early indication of treatment failure and as a therapeutic target

Interpretation: Clinically, galectin-3 concentrations may be categorized into 3 risk categories, substantiated by results from several large chronic heart failure studies: < or =17.8 ng/mL (low risk) 17.9-25.9 ng/mL (intermediate risk) >25.9 ng/mL (higher risk) Results should be interpreted in the context of the individual patient presentation. Elevated galectin-3 results indicate an increased risk for adverse outcomes and signal the presence of galectin-3-mediated fibrosis and adverse remodeling. Once galectin-3 concentrations are elevated they are relatively stable over time in the absence of intervention. Knowledge of a heart failure patient's galectin-3 results may assist in risk stratification and lead to more aggressive management. There are no specific galectin-3 inhibitors available at this time and heart failure patients with elevated galectin-3 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers (ARBs) and aldosterone antagonists are thought to be particularly effective. A large multicenter, prospective, observational study was conducted to derive the reference intervals for galectin-3 that included 1,092 subjects between the ages of 55 and 80 years without any known cardiac disease (520 males, 572 females). The 97.5th percentile of galectin-3 in that cohort was 22.1 ng/mL. Individuals with concentrations greater than 22.1 ng/mL had a significant association with mortality and New York Heart Association (NYHA) classification. However, this was an older population and definitive evidence of cardiac disease was not documented.

Reference Values:
<24 months: not established
2-17 years: < or =25.0 ng/mL
> or =18 years: < or =22.1 ng/mL


**Gamma-Glutamyltransferase (GGT), Serum**

**Clinical Information:** Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Small amounts are present in other tissues. Even though renal tissue has the highest level of GGT, the enzyme present in the serum appears to originate primarily from the hepatobiliary system, and GGT activity is elevated in any and all forms of liver disease. It is highest in cases of intra- or posthepatic biliary obstruction, reaching levels some 5 to 30 times normal. GGT is more sensitive than alkaline phosphatase (ALP), leucine aminopeptidase, aspartate transaminase, and alanine aminotransferase in detecting obstructive jaundice, cholangitis, and cholecystitis; its rise occurs earlier than with these other enzymes and persists longer. Only modest elevations (2-5 times normal) occur in infectious hepatitis, and in this condition, GGT determinations are less useful diagnostically than are measurements of the transaminases. High elevations of GGT are also observed in patients with either primary or secondary (metastatic) neoplasms. Elevated levels of GGT are noted not only in the sera of patients with alcoholic cirrhosis but also in the majority of sera from persons who are heavy drinkers. Studies have emphasized the value of serum GGT levels in detecting alcohol-induced liver disease. Elevated serum values are also seen in patients receiving drugs such as phenytoin and phenobarbital, and this is thought to reflect induction of new enzyme activity. Normal values are observed in various muscle diseases and in renal failure. Normal values are also seen in cases of skeletal disease, children older than 1 year, and in healthy pregnant women-conditions in which ALP is elevated.

**Useful For:** Diagnosing and monitoring hepatobiliary disease, it is currently the most sensitive enzymatic indicator of liver disease. Ascertain whether observed elevations of alkaline phosphatase are due to skeletal disease (normal gamma-glutamyltransferase: GGT) or reflect the presence of hepatobiliary disease (elevated GGT). A screening test for occult alcoholism.

**Interpretation:** An elevation of gamma-glutamyltransferase (GGT) activity is seen in any and all forms of liver disease, although the highest elevations are seen in intra- or posthepatic biliary obstruction. Elevated values can also indicate alcoholic cirrhosis or individuals who are heavy drinkers. The finding of increased GGT and alkaline phosphatase (ALP) activity is consistent with hepatobiliary disease. The finding of normal GGT activity and increased ALP activity is consistent with skeletal disease.

**Reference Values:**

**Males**
- 0-11 months: <178 U/L
- 12 months-6 years: <21 U/L
- 7-12 years: <24 U/L
- 13-17 years: <43 U/L
- > or =18 years: 8-61 U/L

**Females**
- 0-11 months: <178 U/L
- 12 months-6 years: <21 U/L
- 7-12 years: <24 U/L
- 13-17 years: <26 U/L
- > or =18 years: 5-36 U/L

**Clinical References:** 1. Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood.
FGHSP 58034  
**Gamma-Hydroxybutyric Acid (GHB), Serum/Plasma**

**Reference Values:**
Reference Range: Negative

Screening threshold: 5.0 ug/mL

FGHSU 58036  
**Gamma-Hydroxybutyric Acid (GHB), Urine**

**Reference Values:**
Reference Range: Negative

Screening threshold: 5.0 ug/mL

FGANP 75518  
**Ganciclovir, Plasma**

**Reference Values:**
0.2 mcg/mL

The reported value may vary based on dilution or weight of the specimen.

FGAGM 58017  
**Ganglioside (Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b) Antibodies**

**Interpretation:** Ganglioside antibodies are associated with diverse peripheral neuropathies. Elevated antibody levels to ganglioside-monosialic acid (GM1) and the neutral glycolipid, asialo-GM1 are associated with motor or sensorimotor neuropathies, particularly multifocal motor neuropathy. Anti-GM1 may occur as IgM (polyclonal or monoclonal) or IgG antibodies. These antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals. GD1a antibodies are associated with different variants of Guillain-Barre syndrome (GBS) particularly acute motor axonal neuropathy while GD1b antibodies are predominantly found in sensory ataxic neuropathy syndrome. Anti-GQ1b antibodies are seen in more than 80 percent of patients with Miller-Fisher syndrome and may be elevated in GBS patients with ophthalmoplegia. The role of isolated anti-GM2 antibodies is unknown. These tests by themselves are not diagnostic and should be used in conjunction with other clinical parameters to confirm disease.

**Reference Values:**
29 IV or less: Negative
30 Å£â—£â—£ 50 IV: Equivocal
51 Å£â—£â—£ 100 IV: Positive
101 IV or greater: Strong Positive

GM1B 83189  
**Ganglioside Antibody Panel, Serum**

**Clinical Information:** Neuropathy patients have variable sensory disturbance (loss or exaggerated sensation including with pain), weakness and autonomic involvements (sweat abnormalities, gastrointestinal dysfunction, and lightheadedness on standing). These symptoms are a result of injury to the distal nerves, roots, and ganglia or their gathering points (nerve plexus in the thighs and arms). Patients may have symmetric or asymmetric involvements of the extremities, trunk, and head including...
extraocular muscles. Subacute onsets and asymmetric involvements favor inflammatory or immune causes over inherited or metabolic forms. Depending on the specific inflammatory or immune mediated causes other parts of the nervous system may also be affected (brain, cerebellum, spinal cord). Nerve conduction and needle electromyography can help to classify the neuropathy as either: 1) primary axonal; 2) primary demyelinating; or 3) mixed axonal and demyelinating. Among the immune-mediated peripheral neuropathies, autoantibodies to gangliosides represent an important class of noncancer-associated autoimmune peripheral neuropathies. Gangliosides are glycosphingolipids that contain sialic acid and are present in many cell types most abundantly within neural tissues along their linings (myelin). Depending on the specific ganglioside autoantibody found and the antibody titer, in the appropriate clinical context, these findings may be supportive of a specific clinical diagnosis and may also be prognostic for treatment response.(1,2) Specifically, in multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, also known as Lewis-Sumner syndrome or multifocal chronic immune demyelinating polyradiculoneuropathy (CIDP), the presence ganglioside autoantibodies, particularly high-titer GM1-IgM autoantibodies, maybe supportive of the diagnosis in the correct clinical context. Furthermore, ganglioside seropositivity has been associated with favorable response to immunotherapy amongst patients suspected to have MMN during the initial clinical evaluation.(1) Additionally, the presence of ganglioside antibodies may support a diagnosis of Guillain-Barre syndrome (GBS) in the appropriate clinical context.(3) GBS is one class of autoimmune peripheral neuropathies, and comprises a spectrum of disorders including acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy. This class of autoimmune neuropathies is generally characterized by an acute onset. Although the diagnosis of these disorders is dependent on clinical evaluation and electrophysiologic studies, assessment of ganglioside antibodies can further support the diagnosis.

**Useful For:** Supporting the diagnosis of an autoimmune neuropathy

**Interpretation:** High titers (>1:8,000) favor the diagnosis of multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor (MADSAM) over motor neuron disease. About 30% to 50% of patients with these clinical syndromes or the pure motor variant of chronic inflammatory demyelinating polyneuropathy have ganglioside autoantibodies. High-antibody titers appear to be a specific, but not sensitive, marker of those related disorders.

**Reference Values:**

**Profile Information:**
- IGG_M: Negative
- IGM_M: Negative
- IGG_A: Negative
- IGM_A: Negative
- IGG_D: Negative
- IGM_D: Negative

**Reflex Information:**
- IGMTS: <1:2000
- IMMTS: <1:4000
- IGATS: <1:16000
- IMATS: <1:8000
- IGDTS: <1:2000
- IMDTS: <1:2000

**Clinical References:**
FGARG 57634

**Garlic IgG**

**Interpretation:**

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

GARL 82760

**Garlic, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to garlic Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's
GASTN

Gastrin Immunostain, Technical Component Only

Clinical Information: Gastrin is a polypeptide hormone produced and secreted by G cells in the antral mucosa of the stomach and in the duodenum and upper jejunum. The hormone is a potent stimulant of acid secretion and also increases gastric motility. Gastrin staining can identify G cells in the antral stomach and help characterize some islet cell tumors and other neuroendocrine tumors.

Useful For: Characterization of islet cell tumors and endocrine tumors of the gastrointestinal tract

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

GAST

Gastrin, Serum

Clinical Information: Gastrin is a peptide hormone produced by mucosal G cells of the gastric antrum. It is synthesized as progastrin, cleaved to progastrin, which undergoes several posttranslational modifications, in particular sulfation, and is finally processed into the mature 34-amino acid, gastrin-34. Gastrin-34 may be cleaved further into the shorter 17-amino acid, gastrin-17. Either may be secreted as a C-terminal amidated or unamidated isoform. A number of additional, smaller gastrin fragments, as well as gastrin molecules with atypical posttranslational modifications (eg, absent sulfation), may also be secreted in small quantities. Gastrin half-life is short, 5 minutes for amidated gastrin-17, and 20 to 25 minutes for amidated gastrin-34. Elimination occurs through peptidase cleavage and renal excretion. Gastrin-17 I (nonsulfated form) and gastrin-17 II (sulfated) appear equipotent. Their biological effects are chiefly associated with the amidated isoforms and consist of promotion of gastric epithelial cell proliferation and differentiation to acid-secreting cells, direct promotion of acid secretion, and indirect stimulation of acid production through histamine release. In addition, gastrin stimulates gastric motility and release of pepsin and intrinsic factor. Most gastrin isoforms with atypical posttranslational modifications and most small gastrin fragments display reduced or absent bioactivity. This assay measures predominately gastrin-17. Larger precursors and smaller fragments have little or no cross-reactivity in the assay. Intraluminal stomach pH is the main factor regulating gastrin production and secretion. Rising gastric pH levels result in increasing serum gastrin levels, while falling pH levels are associated with mounting somatostatin production in gastric D cells. Somatostatin, in turn, downregulates gastrin synthesis and release. Other weaker factors that stimulate gastrin secretion are gastric distention, protein-rich foods, and elevated secretin or serum calcium levels. Serum gastrin levels may also be elevated in gastric distention due to gastric outlet obstruction and in a variety of conditions that lead to real or functional gastric hypo- or achlorhydria (gastrin is secreted in an attempted compensatory response to achlorhydria). These include atrophic gastritis with or without pernicious anemia, a disorder characterized by destruction of acid-secreting (parietal) cells of the stomach; gastric dumping syndrome; and surgically excluded gastric antrum. In atrophic gastritis, the chronic cell-proliferative stimulus of the secondary hypergastrinemia may contribute to the increased gastric cancer risk observed in this condition. Gastrin levels are
pathologically increased in gastrinoma, a type of neuroendocrine tumor that can occur in the pancreas (20%-40%) or in the duodenum (50%-70%). The triad of non-beta islet cell tumor of the pancreas (gastrinoma), hypergastrinemia, and severe ulcer disease is referred to as the Zollinger-Ellison syndrome. Over 50% of gastrinomas are malignant and can metastasize to regional lymph nodes and the liver. About 25% of gastrinomas occur as part of the multiple endocrine neoplasia type 1 (MEN 1) syndrome and are associated with hyperparathyroidism and pituitary adenomas. These MEN 1-associated tumors have been observed to occur at an earlier age than sporadic tumors and often follow a more benign course. Basal and secretin-stimulated serum gastrin measurements are the best laboratory tests for gastrinoma.

**Useful For:** Investigation of patients with achlorhydria or pernicious anemia Investigation of patients suspected of having Zollinger-Ellison syndrome Diagnosis of gastrinoma

**Interpretation:** Achlorhydria is the most common cause of elevated serum gastrin levels. The most common cause for achlorhydria is treatment of gastroduodenal ulcers, nonulcer dyspepsia, or gastroesophageal reflux with proton pump inhibitors (substituted benzimidazoles, eg, omeprazole). Other causes of hypo- and achlorhydria include chronic atrophic gastritis with or without pernicious anemia, gastric ulcer, gastric carcinoma, and previous surgical or traumatic vagotomy. If serum B12 levels are significantly low (<150 ng/L), even if the intrinsic factor blocking antibody tests are negative, a serum gastrin level above the reference range makes it likely the patient is suffering from pernicious anemia. Hypergastrinemia with normal or increased gastric acid secretion is suspicious of a gastrinoma (Zollinger-Ellison syndrome). Gastrin levels less than 100 pg/mL are observed so uncommonly in untreated gastrinoma patients with intact upper gastrointestinal anatomy as to virtually exclude the diagnosis. The majority (>60%) of patients with gastrinoma have very significantly elevated serum gastrin levels (>400 pg/mL). Levels above 1000 pg/mL in a gastric- or duodenal-ulcer patient without previous gastric surgery, on no drugs, who has a basal gastric acid output of greater than 15 mmol/hour (>5 mmol/hour in patients with prior acid-reducing surgery) are considered diagnostic of gastrinoma. If there are any doubts about gastric acid output, an infusion of 0.1 M HCl into the stomach reduces the serum gastrin in patients with achlorhydria, but not in those with gastrinoma. Other conditions that may be associated with hypergastrinemia in the face of normal or increased gastric acid secretion include gastric and, rarely, duodenal ulcers, gastric outlet obstruction, bypassed gastric antrum, and gastric dumping. Occasionally, diabetes mellitus, autonomic neuropathy with gastroparesis, pheochromocytoma, rheumatoid arthritis, thyrotoxicosis, and paraneoplastic syndromes can also result in hypergastrinemia with normal acid secretion. None of these conditions tends to be associated with fasting serum gastrin levels above 400 pg/mL. Levels above 1000 pg/mL are virtually never observed. Several provocative tests can be used to distinguish these patients from individuals with gastrinomas. Patients with gastrinoma, who have normal or only mildly to modestly increased fasting serum gastrin levels, respond with exaggerated serum gastrin increases to intravenous infusions of secretin or calcium. Because of its greater safety, secretin infusion is preferred. The best validated protocol calls for a baseline fasting gastrin measurement, followed by an injection of 2 clinical units of secretin per kg body weight (0.4 microgram/kg) over 1 minute and further serum gastrin specimens at 5-, 10-, 15-, 20-, and 30-minutes postinjection. A peak gastrin increase of more than 200 pg/mL above the baseline value has greater than 85% sensitivity and near 100% specificity for gastrinoma. Secretin or calcium infusion tests are not carried out in the clinical laboratory, but are usually performed at gastroenterology or endocrine testing units under the supervision of a physician. They are progressively being replaced (or supplemented) by imaging procedures, particularly duodenal and pancreatic endoscopic ultrasound. All patients with confirmed gastrinoma should be evaluated for possible multiple endocrine neoplasia type 1 (MEN 1), which is the underlying cause in approximately 25% of cases. If clinical, biochemical, or genetic testing confirms MEN 1, other family members need to be screened.

**Reference Values:**

<100 pg/mL

There is no evidence that fasting serum gastrin levels differ between adults and children. Although 8-hour fasts are difficult or impossible to enforce in small children, serum gastrin levels after shorter fasting periods (3-8 hours) may be 50% to 60% higher than the 8-hour fasting value.

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

**Clinical References:** 1. Ellison EC, Johnson JA: The Zollinger-Ellison syndrome: a

Gastrointestinal Pathogen Panel, PCR, Feces

Clinical Information: Acute diarrheal syndromes are usually self-limiting but may be complicated by dehydration, vomiting, and fever. Diagnostic testing and treatment may be required in some instances. Many bacterial enteric infections in the United States originate within the food supply chain. According to the CDC, in 2012 there were 19,531 laboratory-confirmed cases of infection with pathogens potentially transmitted through food in the United States. The numbers of infections, by pathogen, were as follows: Salmonella species (7800), Campylobacter species (6793), Shigella species (2138), Cryptosporidium species (1234), Shiga toxin-producing Escherichia coli non-O157 (551), Shiga toxin-producing E coli O157 (531), Vibrio species (193), Yersinia species (155), and Cyclospora cayetanensis (15). Giardia may also be transmitted through ingestion of contaminated food and water. There were 15,178 cases of giardiasis reported to the CDC in 2012. Since the clinical presentation may be very similar to many of these bacterial, viral, and parasitic pathogens, laboratory testing is required for definitive identification of the causative agent. Rapid multiplex panel detection of the most common agents of bacterial, viral, and parasitic enteric infections directly from stool specimens is sensitive, specific, and provides same-day results, obviating the need for culture, antigen testing, microscopy, or individual nucleic acid amplification tests. For other diagnostic tests that may be of value in evaluating patients with diarrhea the following are available in Special Instructions: -Parasitic Investigation of Stool Specimens Algorithm -Laboratory Testing for Infectious Causes of Diarrhea

Useful For: Rapid detection of gastrointestinal infections caused by: -Campylobacter species (Campylobacter jejuni/Campylobacter coli/Campylobacter upsaliensis) -Clostridioides difficile toxin A/B -Plesiomonas shigelloides -Salmonella species -Vibrio species (Vibrio para-haemolyticus, Vibrio vulnificus, Vibrio cholerae) -Vibrio cholerae-Yersinia species -Enteraggregative Escherichia coli (EAEC) -Enteropathogenic E coli non-O157 (EPEC) -Enterotoxigenic E coli (ETEC) -Shiga toxin -E coli O157 -Shigella/Enteroinvasive E coli (EIPEC) -Cryptosporidium species -Cyclospora cayetanensis -Entamoeba histolytica -Giardia -Adenovirus F 40/41 -Astrovirus -Norovirus GI/GII -Rotavirus A -Sapovirus This test is not recommended as a test of cure.

Interpretation: A negative result should not rule-out infection in patients with a high pretest probability for gastrointestinal infection. The assay does not test for all potential infectious agents of diarrheal disease. Positive results do not distinguish between a viable or replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not contained within the panel. Results of the panel are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. In some cases, there may be local public health requirements that impact Mayo Clinic Laboratories (MCL) clients and require additional testing on specimens with positive results from this panel. Clients should familiarize themselves with local requirements. MCL recommends clients retain an aliquot of each specimen submitted for this test to perform additional testing themselves, as needed. If necessary, selected add-on tests can be performed by MCL at an additional charge, as detailed below. Call 800-533-1710 within 96 hours of specimen collection to request supplemental testing for positive test results: Gastrointestinal Pathogen Panel Positive for Client Action Campylobacter species Request add on test: CAMPC / Campylobacter Culture, Feces Salmonella species Request add on test: SALMC / Salmonella Culture, Feces Shigella/Enteroinvasive E coli Request add on test: SHIGC / Shigella Culture, Feces (for...
the Shigella/Enteroinvasive E coli target, the culture will assess for Shigella species only) Yersinia species
Request add on test: YERSC / Yersinia Culture, Feces Vibrio species Request add on test: VIBC / Vibrio
Culture, Feces Shiga toxin-producing E coli E coli O157 Request add on test: E157C / Escherichia coli
O157:H7 Culture, Feces MCL will report results to the client for additional cultures when ordered. If
cultures are positive and the client is in need of the isolated organism (eg, Campylobacter, Salmonella,
Shigella, Yersinia or Vibrio species, or E coli O157:H7) for submission to a public health laboratory, the
client needs to call MCL and request that the isolates be returned to them (the client). The client will be
responsible for submitting the isolates to the appropriate public health department. Positive culture results
will also be reported via the Electronic Clinical Laboratory Reporting System (ECLRS). Alternatively
(not preferred), clients who want a patient specimen returned from MCL should call 800-533-1710 as
soon as possible, at the latest within 96 hours of specimen collection, to request that MCL return an
aliquot of the submitted specimen to them. Clients will be responsible for submitting specimens to
appropriate public health departments.

Reference Values:
Negative (for all targets)

commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool
Prevention: Incidence and trends of infection with pathogens transmitted commonly through
food-foodborne diseases active surveillance network. 10 U.S. sites, 1996-2012. MMWR Morb Mortal
Lawson PA, Citron DM, Tyrrell KL, Finegold SM: Reclassification of Clostridium difficile as
previously effectively, but not validly, published. IJSEM. 2016;66:3761-3764. doi:
10.1099/ijsem.0.001321

**GISTP**

**Gastrointestinal Stromal Tumor (GIST) Targeted Gene Panel, Next-Generation Sequencing, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs
that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor
growth and progression. Multiple targeted therapies have been approved by the Food and Drug
Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to
identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated
risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify
alterations across numerous genes known to be associated with response or resistance to specific
targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess
for common variations in the KIT and PDGFRA genes known to be associated with gastrointestinal
stromal tumors (GIST). The results of this test can be useful for assessing prognosis and guiding
treatment of individuals with GIST.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors This test is
not useful for assessment of hematologic malignancies or germline alterations.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:** 1. Schildhaus HU, Cavlar T, Binot E, et al: Inflammatory fibroid polyps
harbour mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene. J Pathol.
germ-line KIT mutation in a large kindred with gastrointestinal stromal tumors, hyperpigmentation, and
GATA3

70440

**GATA Binding Protein 3 Immunostain, Technical Component Only**

**Clinical Information:** GATA-binding protein 3 (GATA3) is a transcription factor of the GATA family. GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system. GATA3 has been shown to be a useful in the characterization of carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors (ie, paragangliomas).

**Useful For:** Characterizing carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

GATA2

65481

**GATA-Binding Protein 2 (GATA2), Full Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** GATA-binding protein 2 (GATA2) deficiency is emerging as the second most common primary immunodeficiency disorder (PIDD) or inborn error of immunity in adults, after common variable immunodeficiency (CVID). There is a spectrum of clinical presentations associated with GATA2 deficiency, including severe viral infections (eg, human papillomavirus [HPV]), warts, fungal infections, bacterial infections (eg, atypical mycobacterial infections such as nontuberculous mycobacterial infections [NTM] or mycobacterium avium complex [MAC]), myelodysplastic syndrome (MDS), acute myeloid
leukemia (AML), and Emberger syndrome (primary lymphedema with MDS). Other clinical phenotypes of GATA2 deficiency may include aplastic anemia, pulmonary alveolar proteinosis (PAP), sensorineural hearing loss, neutropenia, and congenital lymphedema without MDS at diagnosis. Immunological phenotypes include dendritic cell, monocyte, CD4+ T cell, B and natural killer (NK) cell deficiencies. Also, the loss of a specific NK-cell subset, CD56 bright NK cells, has been reported in these patients. GATA2 deficiency was first described in 2011 as being associated with either MonoMAC (monocytopenia and mycobacterial infection) syndrome or DCML deficiency (dendritic cell, monocyte, B and NK cell lymphocyte deficiency). GATA2 is a zinc finger transcription factor, involved in the generation and function of hematopoietic stem cell progenitors and, therefore, affects several of the subsequent cell lineages. GATA2 deficiency is a disease of haploinsufficiency, and most germline variants appear to arise de novo (spontaneously) but are then transmitted in an autosomal dominant manner. Standard genotype-phenotype correlations are difficult to make, as there is considerable clinical heterogeneity and the age of presentation varies from early childhood to late in adult life. Additionally, there may be a role for environmental factors triggering certain infectious manifestations. There has been incomplete penetrance (not every individual with a variant has a clinical phenotype) observed with GATA2 deficiency as well as variable expressivity (different clinical presentations for the same genetic variant).

The genetic alterations observed in GATA2 are heterogeneous, and include missense variants, nonsense variants, and variants in the regulatory region of intron 5, in-frame deletions involving the C-terminal zinc finger domain, frameshift variants, and large deletions. The latter are associated with null alleles, while regulatory variants have been observed in the enhancer region of intron 5. Somatic variants in ASXL1 have been reported in GATA2 deficiency patients and have been postulated to be associated with transformation to myeloid leukemia. The definitive treatment for GATA2 deficiency is hematopoietic cell transplantation (HCT). Additionally, systemic use of interferon-alpha may be helpful in patients with NK cell deficiency who have recurrent or severe HPV or herpes virus infections. Also, prophylactic antibiotics may be needed or mandated in the nontransplanted patient. The pulmonary alveolar proteinosis observed in GATA2 deficiency is in the context of negative results for anti-GM-CSF autoantibodies has been shown to improve after HCT and suggests correction of alveolar macrophage function. Early genetic diagnosis of GATA2 deficiency is critical in determining strategies for managing the disease considering the broad clinical spectrum. Genetic diagnosis by confirmation of a pathogenic GATA2 variant may also aid in family counseling and screening.

**Useful For:**
A comprehensive evaluation of the GATA2 gene in patients with clinical or immunological symptoms suggestive of GATA-binding protein 2 (GATA2) deficiency Screening family members of patients with confirmed GATA2 deficiency

**Interpretation:**
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
GATA-Binding Protein 3 Immunostain, Technical Component Only, Bone Marrow,

**Clinical Information:** GATA-binding protein 3 (GATA3) is a transcription factor of the GATA family. GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system. GATA3 has been shown to be a useful in the characterization of carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors (ie, paragangliomas).

**Useful For:** Characterizing carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Gaucher Disease, Full Gene Analysis, Varies

**Clinical Information:** Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Reduced or absent activity of this enzyme results in accumulation of its substrate in lysosomes, interfering with cell function. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). In addition, there are 2 rare presentations of Gaucher disease: a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Gaucher disease demonstrates large clinical variability, even within families. Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1:18. There is a broad spectrum of disease in type 1 Gaucher disease, with some patients exhibiting severe symptoms and others very mild disease. Type 1 disease does not involve nervous system dysfunction; patients may display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. Type 2 is characterized by early-onset neurologic disease with rapid progression to death by 2 to 4 years of age. Type 3 may have early onset of symptoms, but generally a slower disease progression than type 2. Alterations in the GBA gene cause the clinical manifestations of Gaucher disease. Over 250 variants have been reported to date. The N370S and L444P alterations have the highest prevalence in most populations. N370S is associated with type 1 Gaucher disease, and individuals with at least 1 copy of this alteration do
not develop the primary neurologic disease seen in types 2 and 3. Conversely, L444P is associated with
neurologic disease. Alterations in the GBA gene have also been reported to cause an increased risk for
Parkinson disease. Alterations associated with Parkinson disease, but not Gaucher disease, are not
routinely reported for patients under the age of 18, but are available upon request. For carrier screening of
the general population, the recommended test is GAUP / Gaucher Disease, Mutation Analysis, GBA,
Varies, which tests for the 8 most common GBA alterations. For diagnostic testing (ie, potentially
affected individuals), enzyme testing (GBAW / Beta-Glucosidase, Leukocytes) should be performed prior
to variant analysis. In individuals with abnormal enzyme activity and 1 or no variants detected by a panel
of common alterations, sequence analysis of the GBA gene should be utilized to detect private variants.
Additionally, measurement of the glucopsychosine biomarker can aid in diagnosis and ongoing
therapeutic monitoring (GPSY / Glucopsychosine, Blood Spot).

Useful For: Confirmation of a diagnosis of Gaucher disease Carrier screening in cases where there is
a family history of Gaucher disease, but an affected individual is not available for testing or
disease-causing alterations have not been identified

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

Reference Values: An interpretive report will be provided.

interpretation of sequence variants: a joint consensus recommendation of the American College of
Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015
Mar;75(2):116-124 3. Hruska KS, LaMarca ME, Scott CR, Sidransky E: Gaucher disease: mutation and
polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat. 2008 May;29(5):567-583

Gaucher Disease, Mutation Analysis, GBA,Varies

Clinical Information: Gaucher disease is a relatively rare lysosomal storage disorder resulting from
a deficiency of beta-glucocerebrosidase. Mutations within the beta-glucocerebrosidase gene (GBA)
cause the clinical manifestations of Gaucher disease. There are 3 major types of Gaucher disease:
nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). Type 1 Gaucher
disease occurs most frequently and is the presentation commonly found among Ashkenazi Jewish
patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1 in 18. Type 1
disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels,
massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. The clinical
variability in type 1 disease is large, with some patients exhibiting severe disease and others very mild
disease. Eight GBA mutations, including the N370S mutation found most commonly in the Ashkenazi
Jewish population, are included in this test: delta 55bp, V394L, N370S, IVS2+1, 84GG, R496H, L444P,
and D409H. This testing panel provides a 95% detection rate for the Ashkenazi Jewish population and
up to a 60% detection rate for the non-Ashkenazi Jewish population. Alternatively, full gene sequencing
is available to evaluate for mutations in all coding regions and exon/intron boundaries of the GBA gene
by ordering GBAZ / Gaucher Disease, Full Gene Analysis.

Useful For: Confirmation of a suspected clinical diagnosis of Gaucher disease Carrier testing for
individuals of Ashkenazi Jewish ancestry or who have a family history of Gaucher disease Prenatal
diagnosis of Gaucher disease in at-risk pregnancies

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

**GCDF**

**GCDFP-15 Immunostain, Technical Component Only**

**Clinical Information:** Immunohistochemical staining with the monoclonal antibody gross cystic disease fluid protein 15 (GCDFP-15) produces diffuse, granular cytoplasmic staining in apocrine sweat glands, normal breast epithelial cells, and breast carcinoma malignant cells. Other neoplasms expressing GCDFP-15 are extramammary Paget disease and carcinomas of the salivary glands, sweat glands, and prostate. A heterogeneous staining pattern, often with paranuclear enhancement, is usually obtained in breast carcinoma.

**Useful For:** Aiding in the identification of extramammary Paget disease, carcinomas of the salivary glands, sweat glands, and prostate

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FGPE**

**Gelatin Porcine IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**GELA**

**Gelatin, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to gelatin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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Reference values apply to all ages.


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**Gelsolin (GSN) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, fibrinogen alpha chain, cystatin C, lysozyme, and gelsolin. Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Gelsolin (GSN) amyloidosis (amyloidosis V) is characterized by corneal lattice dystrophy, cranial neuropathy, and skin changes. Peripheral neuropathy may be present but is typically mild. Like the other hereditary amyloidoses, it is an autosomal dominant disorder; however, homozygosity has been reported and is associated with accelerated renal disease. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.
Useful For: Diagnostic confirmation of amyloidosis V

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

Reference Values:
An interpretive report will be provided.


GBETH 607434

General Factor Bethesda Units, Plasma

Clinical Information: Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

Useful For: Detecting and quantifying the presence and titer of a specific factor inhibitor directed against a specific coagulation factor

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as a reflex. For more information see:
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma
2INHE / Factor II Inhibitor Evaluation, Plasma
7INHE / Factor VII Inhibitor Evaluation, Plasma
10INE / Factor X Inhibitor Evaluation, Plasma
11INE / Factor XI Inhibitor Evaluation, Plasma
< or =0.5 Bethesda Units


FGENT 57728

Gentamicin in Cerebrospinal Fluid (CSF)

Reference Values:
Reference Range: Not Established

Units: ug/mL
Gentamicin, Peak, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of less than or equal to 4 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of less than or equal to 500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 and 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of drug clearance during gentamicin therapy

Interpretation: Goal levels depend on the type of infection being treated. Peak targets are generally between 5.0 and 8.0 mcg/mL for less severe infections and 8.0 and 10.0 mcg/mL for severe infections. Prolonged exposure to peak levels exceeding 12.0 mcg/mL may lead to toxicity.

Reference Values:
Peak: 3.0-12.0 mcg/mL
Toxic peak: >12.0 mcg/mL


Gentamicin, Random, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of less than or equal to 4.0 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of less than or equal to 500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of serum concentration during gentamicin therapy in specimens for which no collection timing information is provided

Interpretation: Goal peak concentrations levels depend on the type of infection being treated. Goal trough levels should be less than 2.0 mcg/mL. Peak targets are generally between 3.0 and 12.0 mcg/mL for conventional dosing. Prolonged exposure to either peak levels exceeding 12.0 mcg/mL or to trough
levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
Gentamicin, Peak  
Therapeutic: 3.0-12.0 mcg/mL  
Toxic: >12.0 mcg/mL  
Gentamicin, Trough  
Therapeutic: <2.0 mcg/mL  
Toxic: >2.0 mcg/mL


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**GENTA 37043**

**Gentamicin, Trough, Serum**

**Clinical Information:** Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of 4.0 mcg/mL or less is considered susceptible for gram-negative bacilli. A MIC of 500 mcg/mL or less is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infection. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of drug clearance during gentamicin therapy

**Interpretation:** Goal levels depend on the type of infection being treated. Goal trough levels should be less than 2.0 mcg/mL for conventional dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
Therapeutic: <2.0 mcg/mL  
Toxic: >2.0 mcg/mL


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**GERB 82545**

**Gerbil Epithelium, IgE, Serum**

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

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

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

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**Germ Cell Tumor (GCT), Isochromosome 12p, FISH, Tissue**

**Clinical Information:** Germ cell tumors (GCT) comprise a heterogeneous group of solid neoplasms that arise in midline locations including the gonads, retroperitoneum, mediastinum, and central nervous system. GCT are categorized based upon their histologic differentiation and can be separated into 2 classes. Seminomatous GCT include seminoma of the testis, dysgerminoma of the ovaries, and germinoma of the brain. Nonseminomatous GCT include yolk sac tumor, embryonal carcinoma, choriocarcinoma, immature teratoma, and mixed forms. Due to the wide spectrum of histologic features observed in these tumors, distinction from non-GCT can be difficult. GCT are often very responsive to chemotherapy and have a better outcome relative to histologically similar malignancies. Thus, distinguishing GCT from non-GCT is critical to providing the appropriate treatment for the patient. Gain of the short arm of chromosome 12, most commonly as an isochromosome 12p[i(12p)], is a highly nonrandom chromosomal marker seen in a significant percentage of GCT. While i(12p) is not 100% specific for GCT, the literature indicates it has diagnostic and possible therapeutic relevance for patients with these tumors. Testing of i(12p) should be concomitant with histologic evaluation, and positive results may support the diagnosis of GCT.

**Useful For:** Supporting the diagnosis of germ cell tumors when used in conjunction with an anatomic pathology consultation
Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the i(12p) probe set. A positive result is consistent with the diagnosis of a germ cell tumors (GCT). A negative result suggests that the i(12p) marker is not present, but does not exclude the diagnosis of a GCT.

Reference Values:
An interpretive report will be provided.


Germinal Center B-cell Expressed Transcript 1 Immunostain, Technical Component Only

Clinical Information: Germinal center B-cell expressed transcript 1 (GCET1), is also known as Centerin and SERPIN9 (serine protease inhibitor). GCET1 is expressed in B cells in the germinal center of normal lymph node and tonsil tissues. Most follicular lymphomas strongly express GCET1. In addition, a proportion of diffuse large B-cell lymphomas (DLBCL) are positive. In the diagnosis of B-cell lymphomas, GCET1 can be useful in an immunohistochemical panel to assign a germinal center phenotype.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


Ghrelin Total, Plasma

Clinical Information: Ghrelin is a novel 28 amino acid peptide derived by post-translational processes from a preproghrelin consisting of 117 residues, secreted by the stomach with specific receptors in the brain involved in appetite regulation. It conveys information to the brain thereby increasing appetite, food intake and body weight and influences the release of growth hormone. Ghrelin is a growth hormone-releasing peptide which acts as an endogenous ligand of the growth hormone secretagogue receptors (GHS-Rs). Ghrelin levels are inversely correlated with body weight and are higher during weight loss.

Reference Values:
Ghrelin (Total): pg/mL
(Plasma)
Adult Reference Range(s)

Normal weight/control subjects: 520 - 700 pg/mL

Obese subjects prior to diet: 340 - 450 pg/mL
Levels:
8:00 am - 12:00 pm: Up to 420 pg/mL
6:00 pm: Up to 480 pg/mL

Obese subjects post induced weight loss: 450 - 600 pg/mL
Levels:
8:00 am - 12:00 pm: Up to 575 pg/mL
6:00 pm: Up to 600 pg/mL

Obese subjects post gastric-bypass surgery: Up to 120 pg/mL

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Giant Ragweed, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to giant ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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| 6             | > or =100      | Strongly positive Reference values apply to all ages.

Giardia Antigen, Feces

Clinical Information: Giardia duodenalis (also known as G lamblia, G intestinalis) is a flagellated protozoan parasite found in contaminated natural streams, lakes, and surface water municipal reservoirs. Humans become infected when ingesting the environmentally resistant cysts in water, food, and by the fecal-oral route. Giardia infects the small intestine by attaching to the mucosa with a ventral sucking disc. Infection may be associated with a variety of outcomes ranging from asymptomatic disease (estimated to occur in 50% of infected individuals) to acute and chronic giardiasis. When present, symptoms generally appear 7 to 14 days after infection, and consist of watery diarrhea, malaise, malodorous steatorrhea, flatulence, abdominal cramping, nausea or vomiting, weight loss, and low grade fever. Less commonly patients experience constipation and urticaria. Symptoms will resolve in most patients after a period of several weeks. However, approximately 15% to 20% will remain chronically infected without treatment and experience ongoing loose stools, weight loss, malabsorption, steatorrhea, abdominal cramping, flatulence, and burping. Longstanding malabsorption may result in vitamin deficiencies and hypoalbuminemia. Acquired lactose intolerance may also occur, and may persist for months after successful parasite eradication. Giardiasis is the most common intestinal parasitic infection in the United States that is reported to the CDC and is a common cause of diarrhea in children (especially in day care centers), travelers, and campers or hikers. It is also responsible for waterborne epidemics. Although Giardia parasites (cysts and trophozoites) may be seen using the microscopy-based stool parasitic exam (OAP / Parasitic Examination, Feces), this is an insensitive method for detection and requires examination of three or more specimens. Instead, detection of parasite antigen or DNA is recommended for optimal sensitivity. The Giardia antigen test (GIAR / Giardia Antigen, Feces) is ideal for settings in which giardiasis is specificallysuspected (egÂ outbreak scenarios), whereas the multiplex gastrointestinal PCR panel (GIP / Gastrointestinal Pathogen Panel, PCR, Feces) is better suited for evaluating multiple potential causes of diarrhea, including parasitic, viral and bacterial pathogens. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

Useful For: Sensitive screening for the detection of Giardia antigens present in fecal specimens

Interpretation: A positive enzyme-linked immunosorbent assay (ELISA) indicates the presence in a fecal specimen of Giardia antigens. As per the manufacturer, the assay has a sensitivity of 96%, specificity of 97%, and a positive predictive value of 95%. Interpretation of results should be correlated with patient symptoms and clinical picture.

Reference Values:
Negative


Ginger, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
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**Useful For:** Establishing the diagnosis of an allergy to ginger Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

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

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Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy.(1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation.(2) Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type 1 diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific
HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tTG, have increased sensitivity and specificity for celiac disease. The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to test TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a study conducted at Mayo Clinic. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. The treatment for celiac disease is maintenance of a gluten-free diet. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. Useful For: Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet Interpretation: Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. Reference Values: Negative: <20.0 U Weak positive: 20.0-30.0 U Positive: >30.0 U Reference values apply to all ages. Clinical References: 1. Green PH, Cellier C: Celiac disease. New Engl J Med 2007;357:1731-1743 2. Green PH, Jabri B: Celiac disease. Annu Rev Med 2006;57:207-221 3. Harrison MS, Wehbi M, Obideen K: Celiac disease: More common than you think. Cleve Clin J Med 2007;74:209-215 4. Dale JC, Homburger HA, Masoner DE, et al: Update on celiac disease: New standards and new tests. Mayo Communique 2008;33(6):1-9 S. Rashatka S, Ettore MW, Homburger HA, et al: Comparative usefulness of deamidated gliadin antibody measurements in the diagnosis of celiac disease. Clin Gastroenterol Hepatol 2008 Apr;6(4):426-432 6. Sugai E, Vazquez H, Nachman F, et al: Accuracy of testing for antibodies to synthetic gliadin-related peptides in celiac disease. Clin Gastroenterol Hepatol 2006;4:1112-1117
Gliadin (Deamidated) Antibody, IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures.

Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tTG, have increased sensitivity and specificity for celiac disease. The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to test TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a study conducted at Mayo Clinic. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

Interpretation: Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient
suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

**Reference Values:**
Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.

**Clinical References:**

**Gliadin (Deamidated) Antibody, IgG, Serum**

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins. (1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. (1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. (2) Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. (3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. (1,2) The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. (1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. (3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. (1-3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. (4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. (2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tissue transglutaminase, have increased sensitivity and specificity for celiac disease. (5,6) The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of test DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a recent study conducted at Mayo Clinic. (5) The treatment for celiac disease is maintenance of a gluten-free diet. (1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet.
diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

**Useful For:** Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

**Interpretation:** Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease.

**Reference Values:**
- Negative: <20.0 U
- Weak positive: 20.0-30.0 U
- Positive: >30.0 U

**Clinical References:**

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**GFAP 70443**

**Glial Fibrillary Acidic Protein Immunostain, Technical Component Only**

**Clinical Information:** Glial fibrillary acidic protein (GFAP) is an intermediate filament protein of 52 kDa found in glial cells, astrocytes, and ependymal cells. Immunoperoxidase staining for GFAP produces intense cytoplasmic staining of astrocytes, glial cells, and ependymal cells in normal brain. In neoplastic tissues, GFAP is useful for the identification of glial tumors such as astrocytomas and ependymomas.

**Useful For:** Classification of glial tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
3. Magaki SD, Williams CK, Vinters HV: Glial function (and
Glipizide (Glucotrol)

Reference Values:

Units: ng/mL

Plasma insulin concentrations have been shown to increase only when plasma glipizide concentrations exceeded 200 ng/mL.

Toxic range has not been established.

Globotriaosylsphingosine, Blood

Clinical Information: Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-GAL A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Females who are heterozygous for Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-GAL A activity in the normal range. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few states, early detection of Fabry disease through newborn screening has been implemented. Measurement of alpha-GAL A in leukocytes (AGA / Alpha-Galactosidase, Leukocytes), serum (AGAS / Alpha-Galactosidase, Serum), or blood spots (AGABS / Alpha-Galactosidase, Blood Spot) can reliably diagnose classic or variant Fabry disease in males. Molecular genetic testing is the recommended diagnostic test for females as alpha-GAL A may be in the normal range in an affected female patient. Molecular analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in males and females. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement of LGb3, may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous females, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

Useful For: Diagnosing and monitoring of patients with Fabry disease when a serum specimen is not available. This test is not intended for newborn screening followup.

Interpretation: An elevation of globotriaosylsphingosine (LGb3) is suggestive of Fabry disease.

Reference Values:

Cutoff: < or =0.034 nmol/mL

**Globotriaosylsphingosine, Blood Spot**

**Clinical Information:** Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-GAL A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, in the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Females who are heterozygous for Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-GAL A activity in the normal range. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and early detection of Fabry disease through newborn screening has been implemented in a few US states. Absent or reduced alpha-GAL A in leukocytes (AGA / Alpha-Galactosidase, Leukocytes), serum (AGAS / Alpha-Galactosidase, Serum), or blood spots (AGABS / Alpha-Galactosidase, Blood Spot) can reliably diagnose classic or variant Fabry disease in males. Molecular genetic testing is the recommended diagnostic test for females as alpha-GAL A activity may be in the normal range in an affected female patient. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in males and females. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement of LGb3 may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous females, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

**Useful For:** Diagnosing and monitoring of patients with Fabry disease using dried blood spots when a serum specimen is not available. This test is not intended for newborn screening followup.

**Interpretation:** An elevation of globotriaosylsphingosine (LGb3) is suggestive of Fabry disease.

**Reference Values:**
Cutoff: ≤ 0.034 nmol/mL

**Clinical References:**

**Globotriaosylsphingosine, Serum**

**Clinical Information:** Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Heterozygous females of Fabry disease can have clinical presentations ranging from...
asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. The estimated incidence varies from 1 in 3,000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing mutation in males and females. Molecular genetic testing is the recommended diagnostic test for females as alpha-galactosidase activity may be in the normal range in an affected female patient. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement of globotriaosylsphingosine (LGb3), may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous females, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

Useful For: Diagnosis and monitoring of Fabry disease

Interpretation: Elevation of globotriaosylsphingosine (Lyso-GB3)is diagnostic for Fabry disease.

Reference Values:
< or =1.0 ng/mL


Glomerular Basement Membrane Antibodies, IgG, Serum

Clinical Information: Antibodies to glomerular basement membrane (GBM) antigens cause glomerulonephritis, Goodpasture syndrome (glomerulonephritis, often with rapid onset renal failure, and pulmonary hemorrhage), and, less commonly, pulmonary hemosiderosis. Nephrogenic GBM antigens are associated with the noncollagenous carboxyl extension of type IV procollagen. The immunologic stimuli that elicit production of GBM antibodies are not known. There is some evidence of a genetic association with HLA-DR2. GBM antibody-mediated glomerulonephritis and Goodpasture syndrome occur with a bimodal age distribution primarily in males ages 20 to 40 and in patients older than age 50. Glomerulonephritis without pulmonary involvement is more common in the older age group, and shows a female predominance.

Useful For: Evaluating patients with rapid onset renal failure or pulmonary hemorrhage, as an aid in the diagnosis of Goodpasture syndrome

Interpretation: Positive results are consistent with Goodpasture syndrome. Glomerular basement membrane antibodies detected by immunoassay have been reported to be highly specific for Goodpasture syndrome. The sensitivity of this test approaches 87% in untreated patients with systemic disease.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.
**Clinical References:** 1. Pusey CD: Anti-glomerular basement membrane disease. Kidney Int 2003;64:1535-1550

### Glucagon Immunostain, Technical Component Only

**Clinical Information:** Glucagon is a polypeptide hormone produced by the (a) cells of the pancreatic islets in response to hypoglycemia or to stimulation by growth hormone. Cytoplasmic staining is seen in pancreatic islet glucagon (a) cells and islet cell tumors. Glucagon is also found in neuroendocrine cells of the small intestine and stomach.

**Useful For:** Aiding in the study of islet-cell tumors and some endocrine tumors of the gastrointestinal tract

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:** N/A


### Glucagon, Plasma

**Clinical Information:** Glucagon is a single-chain polypeptide of 29 amino acids that is derived from a larger precursor peptide (big plasma glucagon) that is cleaved upon secretion. The main sites of glucagon production are the hypothalamus and pancreatic alpha-islet cells. The function of hypothalamic glucagon is incompletely understood and currently no clinical disorders of hypothalamic glucagon function have been defined. Pancreatic islet glucagon is secreted in response to hypoglycemia, with resultant increases in blood glucose concentration. Glucagon's hyperglycemic effect is produced by stimulating hepatic glycogenolysis and gluconeogenesis; it has no effect on muscle glycogen. Once blood glucose levels have normalized, glucagon secretion ceases. Excessive glucagon secretion can lead to hyperglycemia. Excessive and inappropriate glucagon secretion can sometimes be observed in diabetes, in particular during ketoacidosis, and can complicate management of the disorder. In rare cases, it also can occur in tumors of the pancreatic islets (glucagonoma), carcinoid tumors and other neuroendocrine neoplasms, and hepatocellular carcinomas. Patients with glucagon-secreting tumors may present with classic glucagonoma syndrome, consisting of necrolytic migratory erythema, diabetes, and diarrhea but can also have more subtle symptoms and signs. Decreased or absent glucagon response to hypoglycemia can be seen in type I diabetes (insulin-dependent diabetes) and can contribute to severe and prolonged hypoglycemic responses. Glucagon is routinely measured along with serum glucose, insulin, and C-peptide levels, during the mixed-meal test employed in the diagnostic workup of suspected postprandial hypoglycemia. However, it plays only a minor role in the interpretation of this test.

**Useful For:** Diagnosis and follow-up of glucagonomas and other glucagon-producing tumors Assessing diabetic patients with problematic hyper- or hypoglycemic episodes (extremely limited
**Utility**

**Interpretation:** Elevated glucagon levels in the absence of hypoglycemia may indicate the presence of a glucagon-secreting tumor. Successful treatment of a glucagon-secreting tumor is associated with normalization of glucagon levels. Inappropriate elevations in glucagon levels in hyperglycemic type I diabetic patients indicate that paradoxical glucagon release may contribute to disease severity. This can be observed if insulin treatment is inadequate and patients are ketotic. However, glucagon measurement plays little, if any, role in the diagnostic workup of diabetic ketoacidosis, which is based on demonstrating significantly elevated plasma or serum glucose (>250 mg/dL), circulating ketones (beta-hydroxy butyrate), and acidosis (typically with increased anion gap). In diabetic patients, low glucagon levels (undetectable or in the lower quartile of the normal range) in the presence of hypoglycemia indicate impairment of hypoglycemic counter-regulation. These patients may be particularly prone to recurrent hypoglycemia. This can be a permanent problem due to islet alpha-cell destruction or other, less well understood processes (e.g., autonomous neuropathy). It can also be functional, most often due to overt tight blood-glucose control, and may be reversible after decreasing insulin doses.

**Reference Values:**

- `< or =6 hours: 100-650 pg/mL`
- `1-2 days: 70-450 pg/mL`
- `2-4 days: 100-650 pg/mL`
- `4-14 days: declining gradually to adult levels`
- `>14 days: < or =80 pg/mL (range based on 95% confidence limits)`

Glucagon levels are inversely related to blood glucose levels at all ages. This is particularly pronounced at birth and shortly thereafter, until regular feeding patterns are established. This explains the higher levels immediately after birth, which then fall as the glucagon release mobilizes the infant's glucose stores, rise again as stores are depleted, finally normalizing towards adult levels as regular feeding patterns are established.

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

**Clinical References:**

skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy and substrate reduction therapy for types I and III. These treatment options have generally made bone marrow transplantation obsolete. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of Gaucher disease type I ranges from 1 in 30,000 to 1 in 100,000 in the general population but is much more frequent among Ashkenazi Jews with an incidence of approximately 1 in 900. Types II and III both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (BGL / Beta-Glucosidase, Leukocytes), or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) and molecular genetic analysis of the GBA gene (GAUP / Gaucher Disease, Mutation Analysis, GBA, Varies; or GBAZ / Gaucher Disease, Full Gene Analysis, Varies). Lyso GL-1 is a sensitive and specific biomarker for Gaucher disease, and an elevation of lyso GL-1 in blood supports the diagnosis. Lyso GL-1 has also been shown to be helpful in monitoring mildly symptomatic individuals for disease progression and in determining treatment response.

**Useful For:** Second-tier test when newborn screening results with reduced beta-glucosidase (GBA) activity are identified. Diagnosis and monitoring of patients with Gaucher disease. Documentation of an elevated glucosylsphingosine (glucosylsphingosine: lyso-GL1) level supports the biochemical diagnosis of Gaucher disease. Monitoring a patient's response to treatment. This test is not useful for identifying carriers of GBA variants.

**Interpretation:** An elevation of glucosylsphingosine (glucosylsphingosine: lyso-GL1) is indicative of Gaucher disease.

**Reference Values:**
Cutoff: ≤ 0.040 nmol/mL

**Clinical References:**

**Glucosylsphingosine, Blood Spot**

**Clinical Information:** Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-galactosidase, which facilitates the lysosomal degradation of glucosylceramide (glucocerebrosides) and glucosylsphingosine (glucosylsphingosine: lyso-GL1). Gaucher disease is caused by variants in the GBA gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to a mildly symptomatic type. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Gaucher disease type I is the most common form, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease. In addition, Type II
typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and patients may survive into the third and fourth decade. Further subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy or substrate reduction therapy for types I and III. These treatment options have generally made bone marrow transplantation obsolete. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of Gaucher disease type I ranges from 1 in 30,000 to 1 in 100,000 in the general population but is much more frequent among Ashkenazi Jews with an incidence of approximately 1 in 900. Types II and III both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (GBAW / Beta-Glucosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) and molecular genetic analysis of the GBA gene (GAUP / Gaucher Disease, Mutation Analysis, GBA, Varies; or GBAZ / Gaucher Disease, Full Gene Analysis, Varies). Lyso GL-1 is a sensitive and specific biomarker for Gaucher disease, and an elevation of lyso GL-1 in blood supports the diagnosis. Lyso GL-1 has also been shown to be helpful in monitoring mildly symptomatic individuals for disease progression and in determining treatment response.

**Useful For:** Second-tier test when newborn screening results with reduced beta-glucosidase (GBA) activity are identified Diagnosis and monitoring of patients with Gaucher disease using dried blood spot specimens Monitoring a patient's response to treatment This test is not useful for identifying carriers of GBA variants.

**Interpretation:** An elevation of glucopsychosine (glucosylsphingosine: lyso-GL1) is indicative of Gaucher disease.

**Reference Values:**
Cutoff: < or =0.040 nmol/mL

**Clinical References:**

**Glucopsychosine, Plasma**

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abnormalities, lung disease, but no central nervous system involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease. In addition, Type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and patients may survive into the third and fourth decade. Additional subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy and substrate reduction therapy for types I and III. These treatment options have generally made bone marrow transplantation obsolete. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of Gaucher disease type I ranges from 1 in 30,000 to 1 in 100,000 in the general population but is much more frequent among Ashkenazi Jews with an incidence of approximately 1 in 900. Types II and III both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (BGL / Beta-Glucosidase, Leukocytes), or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) and molecular genetic analysis of the GBA gene (GAUP / Gaucher Disease, Mutation Analysis, GBA, Varies; or GBAZ / Gaucher Disease, Full Gene Analysis, Varies). Lyso-GL1 is a sensitive and specific biomarker for Gaucher disease, and an elevation of lyso GL-1 in blood supports the diagnosis. Lyso GL-1 has also been shown to be helpful in monitoring mildly symptomatic individuals for disease progression and in determining treatment response.

**Useful For:** Second-tier test when newborn screening results with reduced beta-glucosidase (GBA) activity are identified Diagnosis and monitoring of patients with Gaucher disease using plasma specimens Documentation of an elevated glucopsychosine (glucosylsphingosine: lyso-GL1) level supports the biochemical diagnosis of Gaucher disease Monitoring a patient's response to treatment This test is not useful for identifying carriers of GBA variants.

**Interpretation:** An elevation of glucopsychosine (glucosylsphingosine: lyso-GL1) is indicative of Gaucher disease.

**Reference Values:**

**GLUCOPSYCHOSINE**

Cutoff: < or =0.003 nmol/mL

**Clinical References:**

**G6PDC**

Glucose 6 Phosphate Dehydrogenase Enzyme Activity, Blood

**Clinical Information:** Hemolytic anemia may be associated with deficiency of erythrocyte enzymes. The most common enzyme defect worldwide is a deficiency of glucose-6-phosphate dehydrogenase (G6PD). As an enzyme in the hexose monophosphate pathway, G6PD plays a key role in the production of NADPH, which is essential for the maintenance of reduced glutathione and the protection of red blood cells from oxidative damage. In patients with G6PD deficiency, the production of NADPH is reduced, leading to increased oxidative stress and hemolysis.

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in the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Because red blood cells lack the citric acid cycle, this NADPH generation is critical for protection against oxidative stress. Normal conditions require approximately 2% of capacity, leaving 98% reserve for stressor events. More than 400 molecular variants of G6PD are known, and the clinical and laboratory features of G6PD deficiency vary according to the degree to which enzyme reserve is decreased. G6PD deficiency (OMIM 300908, X-linked) therefore results in various forms of anemia and is classified by World Health Organization (WHO) criteria according to enzyme activity and chronic versus acute episodic clinical course.(1,2) WHO Classes of G6PD deficiency: Class I: severe, associated with chronic extravascular non-spherocytic hemolytic anemia Class II: severe, associated with episodic acute hemolytic anemia (enzyme level <10%) Class III: moderate, associated with episodic acute hemolytic anemia (enzyme level 10%-60%) Class IV: normal activity (enzyme level 60%-150%). Normal Class V: increased activity (enzyme level >150%). No known clinical sequelae The G6PD locus is located on the X chromosome and, therefore, G6PD deficiency is a sex-linked disorder. Most people with G6PD deficiency are asymptomatic until a stressor event occurs resulting in acute hemolytic anemia that resolves after stimulus removal. Symptoms can include neonatal jaundice (presents at 1-4 days of age) or acute hemolysis triggered by medications (antimalarials, sulfonamides, dapsone, nitrofurantoin, and naphthalene), infection (hepatitis, cytomegalovirus, typhoid), or fava bean ingestion. Hemolysis and jaundice begin 24 to 72 hours after a triggering stimulus, with accompanying dark urine/hemoglobinuria. Anemia worsens for approximately one week and begins to recover ten days after cessation. Splenomegaly, gallstones, and recurrent jaundice are additional clinical symptoms. Because it is X-linked, males are usually more severely affected but homozygous females are seen due to the prevalence of genetic variants. Heterozygous females (carriers) range from asymptomatic to severe anemia due to mosaicism/lyonization. Acquired G6PD may occur due to increasing X inactivation in aging females.(3) Acute episodic G6PD deficiency (WHO class II and III) is not expected to affect length or quality of life. Less commonly seen are genetic variants that result in chronic nonspherocytic hemolytic anemia which manifest similarly to other enzyme deficiencies (WHO class I). The major G6PD variants occur in specific ethnic groups. Thus, knowledge of the ethnic background of the patient is helpful. G6PD deficiency has very high frequency in persons of southeast Asian, African, southern European, and Middle Eastern descent. Rasburicase therapy is contraindicated in patients with G6PD deficiency. Food and Drug Administration (FDA) guidelines state to screen patients at higher risk for G6PD deficiency (eg, patients of African or Mediterranean ancestry) prior to starting therapy.(4) Deficiency can be assessed by enzymatic and/or genetic assays. Due to limitations of genetic testing, in most cases it is preferential to perform G6PD enzyme testing to assign G6PD status. However, enzyme activity can be affected by recent red blood cell transfusion, marked reticulocytosis and very high white blood cell count. In these settings, genotyping may be useful for correlation with the red blood cell enzyme level.(5,6) Due to historic issues with other similar antimalarial medications, questions arise if hydroxychloroquine (HCQ) or chloroquine (CQ) therapy may trigger acute hemolytic episodes in some G6PD subtypes. Data is limited in this regard. Available published data did not find hemolytic episodes associated with HCQ therapy in G6PD deficient African American(7) or CQ therapy in G6PD deficient African(8) patients. Both studied populations were assumed to have mild forms of the disorder. Data regarding these medications in populations with more severe G6PD phenotypes is lacking. While patients receiving HCQ do not routinely need G6PD levels checked before initiating therapy, testing may be considered in patients who are from ethnic backgrounds with high G6PD variant rates such as those from Mediterranean, African, or Asian descent. Although specific details are not described, hemolysis has been reported in at least one individual with G6PD deficiency during the post-approval use of hydroxychloroquine sulfate tablets, United States Pharmacopeia (USP) per FDA label information.(9)

**Useful For:** Evaluation of individuals with episodic or chronic Coombs-negative nonspherocytic hemolytic anemia Rapid testing to assess glucose-6-phosphate dehydrogenase (G6PD) enzyme capacity prior to Rasburicase or other therapies that may cause hemolysis or methemoglobinemia in G6PD deficient patients May aid in the creation of a comprehensive patient profile and can ensure appropriate patient monitoring for developing anemia

**Interpretation:** The World Health Organization (WHO) classification of glucose-6-phosphate dehydrogenase (G6PD) deficiency is historically based on enzyme activity level and in most cases enzyme activity level is sufficient. Accurate classification requires correlation with clinical, and in certain cases, genetic data. Baseline enzyme levels less than 10% of mean normal are either WHO class I
Enzyme levels between 10% and 60% of mean normal can be seen in WHO class III (episodic) variants or female carrier states. Enzyme levels greater than 60% are considered sufficient and can be seen in normal persons, female carrier states or G6PD variants with subclinical effect (WHO class IV). Although G6PD deficiency is an X-linked recessive disorder and most often seen in hemizygous males, some females are affected. In addition, older women who are heterozygous can develop deficiency due to differential X-skewing with age. It is important to note that clinically significant G6PD deficiency can be masked in the setting of significant reticulocytosis, markedly elevated WBC count or recent red blood cell transfusion. If any of these are present in the setting of a history of neonatal, chronic or episodic jaundice or anemia, genotyping for G6PD genetic alterations is recommended. If desired, order G6PDB / Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing, Varies.

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

> or =12 months of age: 8.0-11.9 U/g Hb
Reference values have not been established for patients who are less than 12 months of age.

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women who are heterozygous can develop deficiency due to differential X-skewing with age. It is important to note that clinically significant G6PD deficiency can be masked in the setting of significant reticulocytosis, markedly elevated white blood cell count, or recent red blood cell transfusion. If any of these are present in the setting of a history of neonatal, chronic, or episodic jaundice or anemia, genotyping for G6PD genetic alterations is recommended. If desired, order G6PDB / Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing, Varies.

**Reference Values:**
> or =12 months of age: 8.0-11.9 U/g Hb

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

**Clinical References:**

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**Glucose Phosphate Isomerase Enzyme Activity, Blood**

**Clinical Information:** The glucose 6-phosphate isomerase (GPI) enzyme interconverts glucose 6-phosphate and fructose 6-phosphate in the second step of glycolysis. GPI deficiency (OMIM 613470) is a cause of nonspherocytic hemolytic anemia and has been reported in patients from varied ethnic backgrounds. As investigational methods have improved, the number of confirmed diagnoses has increased, although the disorder remains rare. Inheritance is autosomal recessive. Clinically significant GPI deficiency manifests in variable severity ranging from mild to severe anemia, with jaundice, gallstones and splenomegaly. Some cases of neonatal death/hydrops fetalis have been reported to be associated with GPI deficiency A subset of patients shows neurologic impairment and granulocyte dysfunction. Heterozygotes are expected to have a normal phenotype.

**Useful For:** The evaluation of individuals with Coombs-negative chronic hemolysis

**Interpretation:** Most clinically significant hemolytic anemias due to glucose phosphate isomerase (GPI) deficiency are associated with activity levels less than 30% of mean normal; however, some clinically affected patients can have higher activity due to reticulocytosis. Heterozygotes usually show 40% to 60% of mean normal activity and are hematologically normal. Increased GPI activity is variably seen when young red blood cells are being produced in response to the anemia (reticulocytosis) or in...
newborns.

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

> or =12 months of age: 40.0-58.0 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

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**GPI1**

**Glucose Phosphate Isomerase Enzyme Activity, Blood**

**Clinical Information:** The glucose 6-phosphate (G6P) isomerase enzyme interconverts G6P and fructose-6-phosphate in the second step of glycolysis. Glucose phosphate isomerase (GPI) deficiency (OMIM 613470) is a cause of nonspherocytic hemolytic anemia and has been reported in patients from varied ethnic backgrounds. As investigational methods have improved, the number of confirmed diagnoses has increased, although the disorder remains rare. Inheritance is autosomal recessive. Clinically significant GPI deficiency manifests in variable severity ranging from mild to severe anemia, with jaundice, gallstones, splenomegaly. Some cases of neonatal death/hydrops fetalis have been reported to be associated with GPI deficiency. A subset of patients shows neurologic impairment and granulocyte dysfunction. Heterozygotes are expected to have a normal phenotype.

**Useful For:** The evaluation of individuals with Coombs-negative chronic hemolysis

**Interpretation:** Most clinically significant hemolytic anemias due to glucose phosphate isomerase (GPI) deficiency are associated with activity levels under 30% of mean normal; however, some clinically affected patients can have higher activity due to reticulocytosis. Heterozygotes usually show 40% to 60% of mean normal activity and are hematologically normal. Increased GPI activity is variably seen when young red blood cells are being produced in response to the anemia (reticulocytosis) or in newborns.

**Reference Values:**
> or =12 months: 40.0-58.0 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

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**GLBF**

**Glucose, Body Fluid**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Clinical Information:** Blood glucose is measured to assess the glycemic state of a patient. Body fluid glucose concentrations that are lower than expected indicate increased cellularity and, therefore, glycolysis within the body fluid space. This serves as an indicator of infection or possibly malignancy. Body fluid glucose concentrations are expected to be lower than that found in serum or plasma. Ideally, they are measured in the fasting state, whereby glucose is able to equilibrate into the space the body fluid is contained within. Pleural fluid: Low pleural fluid glucose concentrations (<40-60 mg/dL) indicate a complicated parapneumonic or malignant effusion.(1) However, low glucose is not specific for infection or malignancy and may be attributed to hemothorax, tuberculosis, or rheumatoid or lupus pleuritis, among other diseases. pH is the preferred test for making this determination when available. Pericardial fluid: Pericardial fluid glucose levels have been investigated on a limited basis. In presumed normal specimens collected during surgery, pericardial fluid-to-serum ratio for glucose was 1.0 (95% CI, 0.8-1.2).(2) Peritoneal fluid: Ascitic fluid glucose should be interpreted in conjunction with serum glucose measurement. In a cohort of noninfected patients with alcohol-related cirrhosis, the mean (SD) ascitic fluid-to-serum glucose ratio was 1.04 (0.25).(3) Ascitic fluid glucose may be helpful in differentiating spontaneous bacterial peritonitis from secondary peritonitis caused by bowel perforation.(4) Secondary peritonitis is likely if 2 of the 3 following criteria are met: 1. Total protein is greater than 1 g/dL. 2. Lactate dehydrogenase is greater than 225 IU/L (or greater than the upper limit of normal for serum) 3. Glucose is less than 50 mg/dL.(4) Amniotic fluid: Amniotic fluid is produced by the amnion and placenta, representing a plasma ultrafiltrate. Amniocentesis may be performed to assess fetal distress. Intraamniotic infection or chorioamnionitis is an acute inflammation of the fetal membranes commonly caused by bacterial infection prompting an inflammatory response leading to labor and term or preterm birth.(5) Chorioamnionitis may be symptomatic (clinical) or asymptomatic (histological), occurring most often during prolonged labor or as a consequence of membrane rupture as bacteria have greater opportunity to ascend the lower genital tract to colonize the uterus. Prompt diagnosis and treatment for clinical chorioamnionitis is critical to avoid maternal and fetal morbidity and mortality. Culture and gram stain are often used in the assessment of infection, however, gram stain lacks sensitivity and culture results are not returned in a timely enough manner to make clinical decisions. Low glucose concentrations have been associated with positive culture results and consequently poor outcomes.(6) Synovial fluid: Synovial fluid is present in joint cavities and serves a number of important roles in maintaining joint health and mobility. Symptoms of joint problems include pain, swelling, stiffness, or decreased range of motion. Routine analysis of synovial fluid includes Gram stain, culture, crystal analysis, and cell count with WBC differential. In normal synovial fluid, glucose concentrations are similar to those observed in fasting serum. Low synovial fluid glucose has been associated with septic arthritis or inflammation.(7)

**Useful For:** Aiding in the diagnosis of infection using body fluid specimens

**Interpretation:** Body fluid glucose concentrations may be decreased due to increased cellular metabolism and should be interpreted in the context of blood glucose concentrations and in conjunction with other laboratory and clinical findings.(8, 9) Pleural, peritoneal, and pericardial fluid and serum glucose concentrations are similar in the absence of infection.(3) Transudative pleural fluid glucose concentrations are similar to serum glucose concentrations, while exudates have glucose concentrations less than serum glucose. Glucose levels below 60 mg/dL are typically associated with low fluid pH.(1,10) Amniotic fluid glucose levels below 16 mg/dL is suggestive of infection.(6) Synovial fluid glucose concentrations are similar to fasting blood glucose concentrations or approximately 50% of the nonfasting serum glucose concentration under normal conditions. Values below this can be seen with infection.(7)

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Margaretten ME, Kohlwes J, Moore D: Does this adult patient have septic arthritis? JAMA. 2007;297:1478-1488.

**GLURA**

**Glucose, Random, Serum**

**Clinical Information:** The most common disease related to carbohydrate metabolism is diabetes mellitus, which is characterized by insufficient blood levels of active insulin. Symptoms include polyuria, abnormally elevated blood and urine glucose values, excessive thirst, constant hunger, sudden weight loss, and possibly elevated blood and urine ketones. Complications from diabetes are the third leading cause of death in the United States. There are approximately 16 million diabetics in the United States, and that number is growing. It is estimated that at least 5 million of these people have not been diagnosed. The prevalence in the population age 65 and older is 18.4%, representing 6.3 million cases. The cost of diabetes to the US economy exceeds $92 billion annually. Overproduction or excess administration of insulin causes a decrease in blood glucose to levels below normal. In severe cases, the resulting extreme hypoglycemia is followed by muscular spasm and loss of consciousness, known as insulin shock.

**Useful For:** Diagnosing and managing diabetes mellitus and other carbohydrate metabolism disorders including gestational diabetes, neonatal hypoglycemia, idiopathic hypoglycemia, and pancreatic islet cell carcinoma

**Interpretation:** Any of the following results, confirmed on a subsequent day, can be considered diagnostic for diabetes:
- Fasting plasma or serum glucose > or =126 mg/dL after an 8-hour fast
- 2-Hour plasma or serum glucose > or =200 mg/dL during a 75-gram oral glucose tolerance test (OGTT)
- Random glucose >200 mg/dL, plus typical symptoms

Patients with "impaired" glucose regulation are those whose fasting serum or plasma glucose fall between 101 and 126 mg/dL, or whose 2-hour value on oral glucose tolerance test fall between 140 and 199 mg/dL. These patients have a markedly increased risk of developing type 2 diabetes and should be counseled for lifestyle changes and followed up with more testing. Indications for screening and testing include strong family history, marked obesity, history of babies over 9 pounds, and recurrent skin and genitourinary infections. Glucose levels of 25 mg/dL or lower in infants younger than 1 week are considered to be potentially life threatening, as are glucose levels of 40 mg/dL or lower in infants older than 1 week. Glucose levels of 400 mg/dL and higher are considered a critical value.

**Reference Values:**
- 0-11 months: not established
- > or =1 year: 70-140 mg/dL


**GLUR1**

**Glucose, Random, Urine**

**Clinical Information:** The test is specific for glucose. No other substance excreted in urine is known to give a positive result, including other reducing substances (eg, galactose, fructose, and lactose). This test may be used to determine whether the reducing substance found in urine is glucose. Glucosuria occurs when the renal threshold for glucose is exceeded (typically >180 mg/dL); this is most commonly, although not exclusively, seen in diabetes. However, if the urine glucose is high and the patient is not known to have diabetes mellitus, more specific testing should be considered (fasting blood glucose and/or
Useful For: Limited usefulness for routine screening or management of diabetes mellitus

Interpretation: Small amounts of glucose are normally excreted by the kidney. These amounts are usually below the sensitivity of this test but, on occasion, may produce a color between negative and 100 mg/dL (trace), which is interpreted by the instrument as a positive. Results at the first positive level may be significantly abnormal if found consistently.

Reference Values:
Negative


Glucose, Spinal Fluid

Clinical Information: Cerebrospinal fluid (CSF) is secreted by the choroid plexuses, around the cerebral vessels, and along the walls of the ventricles of the brain, filling the ventricles and cisternae and bathing the spinal cord. CSF is reabsorbed into the blood through the arachnoid villi. CSF turnover is rapid, exchanging about 4 times per day. CSF glucose levels may be decreased due to consumption by microorganisms, impaired glucose transport, or increased glycolysis. Elevated CSF glucose levels are consistent with hyperglycemia.

Useful For: Investigating possible central nervous system infection

Interpretation: Cerebrospinal fluid (CSF) glucose levels may be decreased in any central nervous system infection, although levels are typically normal in viral meningitis, low in bacterial meningitis, and may be normal or low in fungal meningitis. CSF glucose levels are normally about 60% of blood glucose levels.

Reference Values:
Spinal fluid glucose concentration should be approximately 60% of the plasma/serum concentration and should be compared with concurrently measured plasma/serum glucose for adequate clinical interpretation.

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

Clinical References: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Edited by CA Burtis, ER Ashwood, DE Bruns, St. Louis, MO, Elsevier Saunders, 2012

Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing, Varies

Clinical Information: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzymopathy with about 400 million people affected worldwide. It is most commonly found in populations where Plasmodium falciparum malaria is (or was) endemic, but G6PD deficiency may be present in any population. G6PD converts glucose-6-phosphate to 6-phosphoglyconolactone in the first step of the pentose phosphate pathway (PPP), this reaction also produces nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) from nicotinamide adenine dinucleotide phosphate (NADP). NADPH, through subsequent enzymatic reactions, protects erythrocytes from damage by detoxifying hydrogen peroxide and other sources of oxidative stress. G6PD is encoded by the gene G6PD, which lies on the X-chromosome. G6PD deficiency is inherited in an X-linked recessive manner; therefore, males are more commonly affected than females, but due to the high prevalence of G6PD deficiency, homozygous and compound heterozygous females are not uncommon. A large number of G6PD pathogenic variants have been discovered. These variants are subdivided into a class system based on definitions from the World Health Organization (WHO). Table 1. G6PD variant WHO class and
associated G6PD deficiency phenotype WHO class Associated Clinical Presentation G6PD activity I Chronic nonspherocytic hemolytic anemia (CNSHA) <10% II Asymptomatic unless challenged <10% III Asymptomatic unless challenged 10%-60% IV None Normal With the exception of those with chronic nonspherocytic hemolytic anemia (CNSHA), individuals with G6PD deficiency are typically asymptomatic until they are challenged with an exogenous factor such as a drug, infection, or fava beans. The exogenous factor can trigger acute hemolytic anemia (AHA) in individuals with G6PD deficiency. The severity of AHA is highly variable, ranging from mild to life-threatening and can be fatal. Therefore, determining the G6PD deficiency status is recommended on the Food and Drug Administration label of several drugs either proven or suspected to cause AHA in patients with G6PD deficiency. For a list of drugs known to cause AHA in individuals with G6PD deficiency, see Pharmacogenomic Associations Tables in Special Instructions. Preemptive genotyping allows for the identification of patients at risk for an adverse reaction to drugs known to cause AHA in those with G6PD deficiency. In most cases, genotyping provides sufficient information to avoid the use of contraindicated drugs. In some cases, including heterozygous females, the phenotyping assay is necessary to determine if such drugs should be avoided. Skewed X-inactivation in heterozygous females has been reported to result in G6PD deficiency, but the phenotyping assay is necessary to determine G6PD activity level. For more information regarding the need for G6PD enzyme activity follow-up testing to this genotyping assay, refer to the G6PD Genotyping Algorithm for Therapeutic Drug Recommendations in Special Instructions.

Useful For: Genetic test for individuals at high risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency Aiding in the diagnosis of G6PD deficiency Determining G6PD deficiency status in individuals with inconclusive or unexpected phenotyping results Differentiation of heterozygous females with skewed X-inactivation from homozygous and compound heterozygous females Definitive diagnosis of carrier status in females Evaluation of neonates (particularly males) with unexplained jaundice Identifying individuals at risk of drug-induced acute hemolytic anemia (AHA) related to G6PD deficiency

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

Reference Values: An interpretive report will be provided.


**Glucotetrasaccharides, Random, Urine**

**Clinical Information:** Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). This leads to an accumulation of glycogen in the lysosome causing swelling, cell damage, and progressive organ dysfunction. In glycogen storage diseases, excess glycogen is degraded to glucotetrasaccharide (glucose tetrasaccharide: Glc4), which is excreted in urine. Measurement of Glc4 in urine is used for both initial diagnosis and monitoring of patients with Pompe disease and may also be elevated in other glycogen storage disorders. Pompe disease is caused by deleterious variants in the GAA gene. The classic, early infantile onset form of the disease is characterized by progressive muscle hypotonia, weakness, hypertrophic cardiomyopathy, and death due to either cardiorespiratory or respiratory failure, typically by the end of the first year of life. Juvenile and adult-onset forms of Pompe disease are characterized by later development of symptoms and may have milder phenotypes.

**HEX4 64174**

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disease are characterized by later onset and longer survival. Primary symptoms of later-onset Pompe disease include muscle weakness and respiratory insufficiency, with cardiomyopathy only rarely developing. Based on data from newborn screening, the incidence is approximately 1 in 20,000 live births with most patients being affected with later onset forms of Pompe disease. The clinical phenotype depends on residual enzyme activity, with complete loss of activity causing onset in infancy. Enzyme replacement therapy (ERT) improves outcome in many patients with either classic infantile onset or later onset Pompe disease. Early initiation of treatment improves the prognosis and makes early diagnosis of Pompe disease desirable. Because of this, newborn screening for Pompe disease has recently been added to the Recommended Uniform Screening Panel and already been implemented in some states. Historically, diagnostic testing required a skin or muscle biopsy to measure GAA enzyme activity. Today, noninvasive enzyme assays (GAAW / Acid Alpha-Glucosidase, Leukocytes) and molecular genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis, Varies) are available for testing in blood and dried blood spots. In addition, Glc4 can be measured in urine to support a diagnosis of Pompe disease and other glycogen storage disorders.

Useful For: Diagnosing Pompe disease, when used in conjunction with acid alpha-glucosidase enzyme activity assays and molecular genetic analysis of the GAA gene Monitoring Pompe patients on enzyme replacement therapy May support the diagnosis and monitoring of other glycogen storage disorders; however, glucotetrasaccharide (Glc4) excretion appears to be less consistently elevated in glycogen storage disorders other than Pompe disease This test is not useful for carrier screening

Interpretation: An elevated excretion of glucotetrasaccharide is indicative of Pompe disease or other glycogen storage disorders. Enzyme or molecular analysis is required to confirm suspected diagnosis.

Reference Values:
< or =14 months: < or =14.9 mmol/mol Cr
> or =15 months: < or =4.0 mmol/mol Cr

Clinical References:

GLUT-1 Immunostain, Technical Component Only

Clinical Information: Glucose transporter 1 (GLUT-1) is an ubiquitous facilitative membrane glucose transporter that is activated by hypoxia-sensing cellular pathways and may sustain cellular metabolism via glycolysis when hypoxia is present. It is expressed at high levels on erythrocytes, the endothelium of the blood-brain barrier, and the perineurium. Various carcinomas may show overexpression, including fallopian tube carcinomas.

Useful For: Identification of erythrocytes in various normal and neoplastic tissues

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the
patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum**

**Clinical Information:** Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Antibodies directed against the 65-kD isoform of GAD (GAD65) are encountered at high titers (> or =20 nmol/L) in a variety of autoimmune neurologic disorders including stiff-person (Moersch-Woltman) syndrome, autoimmune cerebellitis, brain stem encephalitis, seizure disorders, and other myelopathies. GAD65 antibody is also the major pancreatic islet antibody and an important serological marker of predisposition to type 1 diabetes. GAD65 autoantibody also serves as a marker of predisposition to other autoimmune disease that occur with type 1 diabetes, including thyroid disease (eg, thyrotoxicosis, Grave disease, Hashimoto thyroiditis, hypothyroidism), pernicious anemia, premature ovarian failure, Addison disease, (idiopathic adenocortical failure) and vitiligo. GAD65 antibodies are found in the serum of approximately 8% of healthy subjects older than age 50, usually in low titer but often accompanied by related "thyrogastric" autoantibodies.

**Useful For:**
- Assessing susceptibility to autoimmune (type 1, insulin-dependent) diabetes mellitus and related endocrine disorders (eg, thyroiditis and pernicious anemia)
- Distinguishing between patients with type 1 and type 2 diabetes
- Confirming a diagnosis of stiff-man syndrome, autoimmune encephalitis, autoimmune ataxia, brain stem encephalitis, autoimmune epilepsy, autoimmune myelopathy; titers generally greater than or equal to 20.0 nmol/L

**Interpretation:**
- High titers (> or =20.0 nmol/L) are found in classic stiff-person syndrome (93% positive) and in related autoimmune neurologic disorders (eg, acquired cerebellar ataxia, some acquired non-paraneoplastic encephalomyelopathies). Diabetic patients with polyendocrine disorders also generally have glutamic acid decarboxylase (GAD65) antibody values 0.02 nmol/L or above. Values in patients who have type 1 diabetes without a polyendocrine or autoimmune neurologic syndrome are usually 0.02 nmol/L or below. Low titers (0.03-19.9 nmol/L) are detectable in the serum of approximately 80% of type 1 diabetic patients. Conversely, low titers are detectable in the serum of less than 5% of patients with type 2 diabetes. Testing for autoimmune type 1 diabetes is complimented by testing for insulin, IA-2 and ZnT8 antibodies. Eight percent of healthy Olmsted County residents over age 50 have low-positive values, and may be at risk for future autoimmune disease. Values 0.03 nmol/L or above are consistent with susceptibility to autoimmune (type 1) diabetes and related endocrine disorders (thyroiditis and pernicious anemia).

**Reference Values:**
- < or =0.02 nmol/L

**Clinical References:**
Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid

Clinical Information: Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Serum antibodies directed against the 65-kD isoform of GAD (GAD65) are detected in heightened frequency in a variety of autoimmune neurologic disorders, autoimmune encephalitis, including stiff-person (Moersch-Woltman) syndrome, autoimmune ataxia, and autoimmune epilepsy.

Useful For: Possible use in evaluating patients with autoimmune encephalitis, stiff-person syndrome, autoimmune ataxia, autoimmune epilepsy, and other acquired central nervous system disorders affecting gabaminergic neurotransmission.

Interpretation: Intrathecal synthesis of glutamic acid decarboxylase 65 (GAD65) antibody has been demonstrated in patients with stiff-man syndrome, but cerebrospinal fluid (CSF) values are log orders lower than serum. We have not determined the frequency of GAD65 antibodies in spinal fluid of patients with various diagnoses.

Reference Values:
< or =0.02 nmol/L
Reference values apply to all ages.


Glutamine Synthetase Immunostain, Technical Component Only

Clinical Information: Glutamine synthetase (GS) is an enzyme that catalyzes the ATP-dependent condensation of glutamate with ammonia to form glutamine. GS can be used with a panel of immunohistochemistry markers (beta-catenin, liver fatty acid binding protein, C-reactive protein, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and nonneoplastic liver. GS, a target gene of beta-catenin, is expressed in hepatic adenomas with beta-catenin alterations (type 2), but it is not expressed in hepatic adenomas without beta-catenin alterations. GS is expressed in zone 3 of normal liver and has a characteristic map-like pattern in focal nodular hyperplasia.

Useful For: Classification of hepatic adenomas and the identification of focal nodular hyperplasia.

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Glutaric Aciduria Type II Gene Panel, Varies

Clinical Information: Glutaric acidemia Type II (GA II), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with symptoms including hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA II can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. Three genes have been implicated in causing GA II: ETFA, ETFB, and ETFDH. This comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features of GA II.

Useful For: Follow up for abnormal biochemical results suggestive of glutaric acidemia type II Establishing a molecular diagnosis for patients with glutaric acidemia type II Identifying variants within genes known to be associated with glutaric acidemia, allowing for predictive testing of at-risk family members

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

Reference Values: An interpretive report will be provided.


Glutathione, Blood

Clinical Information: Hemolytic anemia may be associated with deficiency of erythrocyte enzymes. Red blood cell (RBC) enzymes linked to hemolysis are those important in the energy generation of glycolysis or protection from oxidative stress such as the hexose monophosphate shunt. The hexose monophosphate pathway depends primarily upon the glucose 6-phosphate dehydrogenase (G6PD) enzyme for the generation of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) with 6-phosphogluconate dehydrogenase (6PGD) providing an additive effect. Both reactions require adequate levels of reduced glutathione (GSH). Because RBCs lack the citric acid cycle, this is an important source of NADPH, and a deficiency of G6PD or GSH results in the inability to neutralize oxidative insults. GSH is synthesized from amino acids by two enzymatic steps and is present in liver, kidney, brain, muscle, and RBCs. It plays widely versatile and important roles in the synthesis of proteins and DNA, the processing of medications and toxins, and other redox reactions. Similar to G6PD deficiency, glutathione deficiency can have an episodic acute time course of hemolysis or jaundice, be triggered by fava beans, and cause neonatal hyperbilirubinemia. Five enzymes impact GSH availability and therefore are potential candidates for abnormalities leading to glutathione deficiency: -Two enzymes, gamma-glutamylcysteine synthetase (GCLC) and glutathione synthetase (GSS), are required for GSH synthesis -Two enzymes, glutathione reductase (GSR) and glutathione peroxidase (GPX1), are required for reduction-oxidation cycling of oxidized glutathione (GSSG) to reduced glutathione (GSH) -A family of enzymes, glutathione S-transferases (GSTs), utilizes GSH in the detoxification and preparation of substances for excretion into the bile or urine Enzyme deficiencies have been reported in all of these enzymes, albeit very rarely. The
best characterized are GSS and GCLC deficiencies. GSS deficiency is associated with two clinical presentations; a mild form causing isolated chronic hemolytic anemia (OMIM 231900), and a more severe form marked by urinary excretion of 5-oxoproline, metabolic acidosis, hemolytic anemia, and central nervous system disorders (5-oxoprolinuria, OMIM 266130). GCLC deficiency is associated with moderate to severe chronic hemolytic anemia present from neonatal or early childhood, or compensated hemolysis with sporadic but recurrent anemia or jaundice. Some cases have shown learning disabilities, severe and progressive ataxia with myopathy and spinocerebellar degeneration. GSR deficiency has been confirmed in three siblings with favism (episodic hemolysis after fava bean ingestion) and cataracts in early adulthood, and an unrelated infant with marked neonatal hyperbilirubinemia. GSR activity can be decreased in riboflavin deficiency, but whether this results in hemolysis is not clear. Although patients have been reported with anemia in the context of decreased GPX1 activity (OMIM 614164) and decreased GST activity was found in a person with hemolytic anemia, splenomegaly, hyperbilirubinemia, and cholelithiasis, neither have been characterized sufficiently as the definitive cause of hemolysis. All described cases have shown autosomal recessive inheritance pattern. A deficiency of either of the synthetic enzymes, GCLC or GSS, results in GSH levels less than 25%, but many show a virtual absence of measurable GSH. Heterozygotes usually show normal GSH levels. Elevated concentrations of GSH are found in patients with myelofibrosis and in those with pyrimidine-5'-nucleotidase deficiency.

**Useful For:**
- Evaluation of neonatal hyperbilirubinemia, favism or chronic or episodic hemolysis or jaundice
- Evaluation for gamma-glutamylcysteine synthetase deficiency (OMIM 230450)
- Evaluation for glutathione synthetase deficiency causing hemolytic anemia (OMIM 231900)
- Evaluation for generalized glutathione synthetase deficiency with 5-oxoprolinuria (OMIM 266130)

**Interpretation:**
Measurement of reduced glutathione (GSH) is used as a surrogate for the activity of the enzymes that contribute to normal levels of GSH within the red blood cell. GSH is associated with less than 25% of mean normal in individuals with deficiencies of gamma-glutamyl cysteine synthetase or glutathione synthetase. Elevated concentrations of GSH are of uncertain significance. This finding can be nonspecific and is seen in normal neonates, pyrimidine-5<sup>TM</sup>-nucleotidase deficiency, lead poisoning, dyserythropoietic disorders (inherited and acquired), myelofibrosis (possibly due to chromosome 8 duplication), or riboflavin supplementation. Consistently elevated glutathione levels have been reported in a family with mild hemolytic anemia of uncertain cause (1); however, whether this was causative or incidental was not determined.

**Reference Values:**
> or =12 months: 46.9-90.1 mg/dL RBC
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

**FGLUT**
57559
**Gluten IgG**

**Interpretation:**

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Gluten, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to gluten Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>4</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Glycine Receptor Alpha1 IgG, Cell Binding Assay, Serum

Clinical Information: Inhibitory synaptic transmission is mediated by gamma-aminobutyric
acid-ergic (GABA-ergic) and glycinergic spinal interneurons, which regulate motor neuron excitability in the brainstem and spinal cord. Autoimmune central nervous system disorders include classic stiff-man syndrome (also known as stiff-person syndrome), limited stiff-man forms (eg, stiff-limb syndrome) and a severe (and sometimes fatal) encephalomyelitic variant known as progressive encephalomyelitis with rigidity and myoclonus (PERM). These disorders are unified clinically by exaggerated startle, stiffness, and spasms of the axis and/or limbs. Characteristic electrophysiologic findings include continuous motor unit activity by unipolar electromyographic (EMG) recording, and exaggerated and non-habituating acoustic startle responses. Eighty percent of patients are seropositive for antibody targeting the 65 kDa isoform of glutamic acid decarboxylase (GAD65). The alpha-1-subunit of the glycine receptor (GlyRa1), which is enriched in brainstem and spinal cord, has emerged as an antigenic target with specificity for the autoimmune stiff-person spectrum, and is particularly useful for diagnostics among patients seronegative for GAD65-IgG. GlyRa1-IgG has been described among patients with PERM (33%), classic stiff-man syndrome (9%), and limited stiff-man forms (17%). Seropositivity for GlyRa1-IgG is detected in 19% of patients from the stiff-man spectrum who are GAD65-IgG seronegative. The clinical context is usually non-paraneoplastic, though thymoma and lymphomas have been occasionally described. Disease-specific antibodies may be detected in serum only, CSF only, or both. Improvements with immunotherapy (steroids, plasma exchange or intravenous immune globulin) occur more commonly in GlyRa1-IgG seropositive patients than among patients seropositive for GAD65 antibody only. In one series, improvement was noted in 6/7 GlyRa1-IgG antibody positive patients compared with only 7/25 without these antibodies.

**Useful For:** Evaluating patients with suspected autoimmune stiff-person spectrum disorders (stiff-person syndrome, stiff-limb, stiff trunk or progressive encephalomyelitis with rigidity and myoclonus [PERM]) using serum specimens

**Interpretation:** In the appropriate clinical context, this profile is consistent with a stiff-person syndrome spectrum disorder (classical stiff-person, stiff-limb, or progressive encephalomyelitis with rigidity and myoclonus [PERM]). A paraneoplastic cause should be considered.

**Reference Values:**
Negative

**Clinical References:**
described among patients with PERM (33%), classic stiff-man syndrome (9%), and limited stiff-man forms (17%). Seropositivity for GlyRa1-IgG is detected in 19% of patients from the stiff-man spectrum who are GAD65-IgG seronegative. The clinical context is usually non-paraneoplastic, though thymoma and lymphomas have been occasionally described. Disease-specific antibodies may be detected in serum only, CSF only, or both. Improvements with immunotherapy (steroids, plasma exchange or intravenous immune globulin) occur more commonly in GlyRa1-IgG seropositive patients than among patients seropositive for GAD65 antibody only. In one series, improvement was noted in 6/7 GlyRa1-IgG antibody positive patients compared with only 7/25 without these antibodies.

**Useful For:** Evaluating patients with suspected autoimmune stiff-person spectrum disorders (stiff-person syndrome, stiff-limb, stiff trunk, or progressive encephalomyelitis with rigidity and myoclonus [PERM]) using spinal fluids specimens

**Interpretation:** In the appropriate clinical context, this profile is consistent with a stiff-person syndrome spectrum disorder (classical stiff-person, stiff-limb, or progressive encephalomyelitis with rigidity and myoclonus [PERM]). A paraneoplastic cause should be considered.

**Reference Values:**
Negative

**Clinical References:**

**Glycogen Storage Disease Gene Panel, Varies**

**Clinical Information:** Glycogen storage diseases (GSD) are a group of inherited metabolic conditions caused by deficiency of enzymes responsible for glycogen metabolism, resulting in abnormal storage of glycogen in the liver and various muscles. There are over 15 different GSD that vary in symptoms and severity, dependent on the enzyme deficiency, although liver and muscle are most commonly affected. Generally, they can be divided into 2 categories, those with hepatic involvement and those with neuromuscular involvement. Some GSD result in single tissue disease, while others affect multiple organs. Clinical features may include hepatomegaly, hypoglycemia, muscle cramps, exercise intolerance, and progressive fatigue and weakness. Preliminary biochemical testing may be helpful in making a diagnosis (ie, glucose monitoring, triglycerides, uric acid level, creatine kinase, liver function tests, and complete blood cell count). This test involves sequencing of 26 genes related to various GSD.

**Useful For:** Follow up of abnormal biochemical results consistent with glycogen storage disease (GSD) Establishing a molecular diagnosis for patients with GSD Identifying variants within genes known to be associated with GSD allowing for predictive testing of at-risk family members

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
G161
Glycogen Storage Disease Panel (Bill Only)

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

FGLMA
GlycoMark

Reference Values:
Age Range
<18 y Not Established
Adult Males 10.7-32.0
Adult Females 6.8-29.3

GlycoMark is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.
1, 5-AG blood levels can be affected by clinical conditions or medications.

GLYCF
Glycophorin A (CD235a) Immunostain, Technical Component Only

Clinical Information: Glycophorin A is expressed by erythroid precursors in the bone marrow and is also present on erythrocytes. Glycophorin A is useful to characterize erythroid cell development and aid in the diagnosis of erythroid leukemia.

Useful For: Aiding in the identification of erythroid precursors in bone marrow

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
NA

Clinical References:
**Glycyphagus domesticus, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to Glycyphagus domesticus. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode. - To confirm sensitization prior to beginning immunotherapy. - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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

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**Glypican-3 Immunostain, Technical Component Only**

**Clinical Information:** Glypican-3 (GPC3) protein is a member of the glypican family of heparin sulfate proteoglycans that are phosphatidylinositol-anchored to the cytoplasmic membrane. GPC3 acts as a coreceptor for heparin-binding growth factors, which play an important role in cell growth and differentiation. Diagnostically, GPC3 will aid in separating hepatocellular carcinomas from other malignancies and hepatic adenomas. It is expressed in 70% to 90% of hepatocellular carcinomas.

**Useful For:** Differentiating hepatocellular carcinomas from other malignancies and hepatic adenomas.

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation.
or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
N/A

Clinical References:

GNPTAB Gene, Full Gene Analysis, Varies

Clinical Information: N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits (GNPTAB)-related mucolipidoses are progressive lysosomal storage diseases traditionally classified as mucolipidosis II and mucolipidosis III based upon their severity and disease onset. These conditions have substantial clinical overlap and mutation testing can aid the diagnosis. Mucolipidosis II alpha/beta (ML II alpha/beta or I-cell disease) is a progressive inborn error of metabolism with clinical onset at birth and fatal outcome most often in early childhood. Postnatal growth is limited and often ceases in the second year of life; contractures develop in all large joints. The skin is thickened, facial features are coarse, and gingiva are hypertrophic. Orthopedic abnormalities present at birth may include thoracic deformity, kyphosis, clubfeet, deformed long bones, and hip dislocation. There is often cardiac involvement, most commonly thickening and insufficiency of the mitral valve and, less frequently, the aortic valve. Progressive mucosal thickening narrows the airways and gradual stiffening of the thoracic cage contributes to respiratory insufficiency, the most common cause of death. Mucolipidosis III alpha/beta (ML III alpha/beta or pseudo-Hurler polydystrophy) is a slowly progressive disorder with clinical onset at approximately 3 years of age. It is characterized by a slow growth rate and subnormal stature; radiographic evidence of mild-to-moderate dystostosis multiplex; joint stiffness and pain initially in the shoulders, hips, and fingers; gradual mild coarsening of facial features; and normal to mildly impaired cognitive development. If present, organomegaly is mild. Pain from osteoporosis that is clinically and radiologically apparent in childhood becomes more severe from adolescence. Cardiorespiratory complications (restrictive lung disease, thickening and insufficiency of the mitral and aortic valves, left and/or right ventricular hypertrophy) are common causes of death, typically in early to middle adulthood. ML II/ML III alpha/beta are inherited in an autosomal recessive manner. Both disorders have been reported from nearly all parts of the world and the overall carrier rate ranges between 1 in 158 and 1 in 316. GNPTAB is the gene in which mutations are most often known to cause ML II/MLIII alpha/beta. Bidirectional sequencing of the entire GNPTAB coding region detects 2 disease-causing mutations in more than 95% of individuals with ML II/MLIII alpha/beta. This gene encodes 2 of 3 subunits (alpha/beta) of the heterohexameric enzyme, N-acetylglucosamine-1-phosphotransferase. In the absence of this enzyme, a mannose 6-phosphate (M6P) recognition marker is not added to lysosomal hydrolases and other glycoproteins. This leads to disruption of acid hydrolases transport to the lysosome. Formation of the M6P recognition marker on lysosomal hydrolases is significantly reduced in ML III alpha/beta, and nearly or totally absent in ML II alpha/beta. To confirm or establish the diagnosis in a proband requires a combination of clinical evaluation and laboratory testing. The use of the following diagnostic testing is recommended: Identification of characteristic clinical and radiographic findings, assay of oligosaccharides in urine, assay of several acid hydrolases in plasma, sequence analysis of GNPTAB. The activity of nearly all lysosomal hydrolases in plasma and other body fluids is higher in individuals affected with ML II alpha/beta (5- to 20-fold) and ML III alpha/beta (up to 10-fold) than in normal controls. ML II/ML III alpha/beta is diagnosed by assay of N-acetylglucosamine-1-phosphotransferase in skin fibroblasts. Demonstration of nearly complete inactivity (<1%) of the enzyme confirms the diagnosis of ML II.
alpha/beta, whereas significant deficiency (1%-10% of normal) of this enzyme is suggestive of the
diagnosis of ML III alpha/beta. Urinary excretion of oligosaccharides is often excessive. Prior to
molecular analysis, the delineation of ML II alpha/beta from ML III alpha/beta depended solely on
clinical criteria including age of onset, rate of progression, and overall severity. Molecular genetic
studies reveal a genotype-phenotype correlation supporting the clinical distinction between ML II
alpha/beta and ML III alpha/beta. Mutations that completely inactivate the phosphotransferase
consistently result in ML II alpha/beta, irrespective of their location within the gene. Mutations with
less adverse effect on this enzyme activity usually result in ML III alpha/beta or occasionally in
intermediate phenotypes.(1,2)

Useful For: Molecular diagnosis or carrier status of mucolipidosis II alpha/beta and mucolipidosis III
alpha/beta in conjunction with identification of characteristic clinical, radiographic, and biochemical
findings, and genetic counseling for family members

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kudo M, Brem MS, Canfield WM: Mucolipidosis II (I-cell disease) and
mucolipidosis IIIA (classical pseudo-hurler polydystrophy) are caused by mutations in the

GOAT
82783

Goat Epithelium, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to goat epithelium Defining the allergen responsible
for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or
anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the
specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
</tbody>
</table>
GMILK  
**Goat’s Milk, IgE, Serum**

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

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

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

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td></td>
<td>Negative</td>
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<tr>
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<td>0.35-0.69</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Goldenrod, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to goldenrod Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Golimumab and Anti-Golimumab Antibody, DoseASSURE GOL

**Reference Values:**

Golimumab:

Quantitation Limit: <0.5 ug/mL

Results of 0.5 ug/mL or higher indicate detection of Golimumab

In the presence of serum anti-golimumab antibodies, the golimumab drug level reflects the antibody-unbound (free) fraction of golimumab in serum

Anti-Golimumab Antibody:
Quantitation Limit: <20 ng/mL

Results of 20 or higher indicate detection of anti-Golimumab antibodies.

FGNRH
90165

Gonadotropin Releasing Hormone (Gn-RH, Luteinizing Hormone-Releasing Hormone LH-RH)

Clinical Information: Gonadotropin-Releasing Hormone (Gn-RH), also known as Luteinizing Hormone-Releasing Hormone (LH-RH), is a decapeptide secreted pulsatility from the hypothalamus. It stimulates the release of the Gonadotropins - Luteinizing Hormone and Follicle Stimulating Hormone - exerting a stronger effect on Luteinizing Hormone. Testosterone and Estradiol, whose release is stimulated by the Gonadotropins, exert a negative feedback control on LH-RH both at the hypothalamic site and by decreasing pituitary receptor binding. LH-RH levels are low in patients with hypothalamic hypogonadism differentiating them from the high levels usually found in primary hypopituitary hypogonadism. Accentuation of the LH-RH pulse occurs at the onset of puberty triggering the release of LH and FSH required in pubertal development. LH-RH is stimulated by Epinephrine and suppressed by Dopamine and opiates. LH-RH and some of its agonists are frequently used to induce ovulation.

Reference Values:
Adult Reference Range(s):
- Males: 4.0 - 8.0 pg/mL
- Females: 2.0 - 10.0 pg/mL

No pediatric reference ranges available for this test.

Clinical References:

GOOS
82714

Goose Feathers, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to goose feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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

Reference values apply to all ages.


**Gram Stain for Bacterial Vaginosis**

Clinical Information: Bacterial vaginosis is so-named because bacteria are the cause and an associated inflammatory response is lacking. It results in an increase in thin, gray, homogeneous vaginal discharge and vaginal malodor and is caused by a change in the vaginal flora. Bacterial vaginosis is a synergistic polymicrobial infection not caused by a specific organism. The standard scoring system termed the "Nugent score" is a technique for assessing bacterial vaginosis using microscopic examination of a Gram-stained smear of vaginal discharge.

Useful For: Supporting the diagnosis of bacterial vaginosis

Interpretation: Assessment of a Gram-stained slide using the Nugent score has replaced culture as the preferred test to diagnose bacterial vaginosis. (1) While Gardnerella is the most common anaerobe found in bacterial vaginosis, other anaerobic organisms are often present along with a decrease in the amount of "usual flora" (eg, Lactobacillus species). This system uses a 0- to 4-point scale to calculate the weighted sum of the following 3 bacterial morphotypes: Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus species. A total score of greater than 6 is considered abnormal, a total score of 4 to 6 is considered a transitional stage, and a total score of 0 to 3 is considered normal. Clue cells and yeast are also reported, if present.

Reference Values:
One of the 3 following reports dependent on the weighted sum balance of Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus species:
1. Consistent with normal bacterial vaginal flora.
2. Altered vaginal flora not consistent with bacterial vaginosis. This frequently represents a transitional stage. If signs or symptoms persist, repeat testing is warranted.
3. Consistent with bacterial vaginosis.

Clinical References: CAP Microbiology checklist: Bacterial Vaginosis-Evaluation of a criterion-based Gram stain is used for the microscopic diagnosis of bacterial vaginosis. 2011

**Gram Stain, Varies**

Clinical Information: The Gram stain is a general stain used extensively in microbiology for the preliminary differentiation of microbiological organisms. The Gram stain is one of the simplest, least expensive, and most useful of the rapid methods used to identify and classify bacteria. The Gram stain is used to provide preliminary information concerning the type of organisms present directly from clinical
specimens or from growth on culture plates. This stain is used to identify the presence of microorganisms in normally sterile body fluids (cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid). It is also used to screen sputum specimens to establish acceptability for bacterial culture (<25 squamous epithelial cells per field is considered an acceptable specimen for culture) and may reveal the causative organism in bacterial pneumonia.

**Useful For:** Identifying microorganisms in normally sterile body fluids Screening sputum specimens for acceptability for bacterial culture Guiding initial antimicrobial therapy

**Interpretation:** During the staining process, the crystal violet and iodine form a complex within the heat fixed cell. In gram-negative organisms, this complex is readily washed out by the acetone-alcohol. They appear red because they retain only the safranin dye (counterstain). Gram-positive organisms retain the crystal violet-iodine complex after decolorization and remain purple. Cells and Organisms will be reported according to the following tables:

<table>
<thead>
<tr>
<th>White Blood Cells</th>
<th>Epithelial Cells</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Power Field (LPF-10x)</td>
<td>Rare (R) ≤ 1</td>
<td>Oil Immersion Field (OIF-100x) Rare (R) ≤ 1 Few (F) 1-9 Few (F) 1-5 Moderate (O) 10-25 Moderate (O) 6-30 Many (M) &gt;25 Many (M) &gt;30</td>
</tr>
</tbody>
</table>

**Reference Values:**
No organisms seen or descriptive report of observations.


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**Granulocyte Antibodies, Serum**

**Clinical Information:** Granulocyte antibodies are induced by pregnancy or prior transfusion and are associated with febrile, nonhemolytic transfusion reactions. Patients who have been immunized by previous transfusions, pregnancies, or allografts frequently experience febrile, nonhemolytic transfusion reactions which must be distinguished from hemolysis before further transfusions can be safely administered. Granulocyte antibodies may also be present in autoimmune neutropenia.

**Useful For:** The work-up of individuals having febrile, nonhemolytic transfusion reactions The detection of individuals with autoimmune neutropenia

**Interpretation:** A positive result in an individual being worked up for a febrile transfusion reaction indicates the need for leukocyte-poor (filtered) red blood cells. This test cannot distinguish between allo- and autoantibodies

**Reference Values:**
Not applicable


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**Granzyme B Immunostain, Technical Component Only**

**Clinical Information:** Granzyme B is a cytotoxic granule-associated protein, expressed constitutively in natural killer cells and in activated cytotoxic T cells. The immunostain is used to characterize T-cell lymphomas with a cytotoxic phenotype.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the...
context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
NA

**Clinical References:**

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**FGRPG 57653**

**Grape IgG**

**Interpretation:**

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

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**GRAP 82800**

**Grape, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to grape Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Grapefruit, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to grapefruit Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

**Grass Panel # 1, Serum**

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>4</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Grass Panel # 2, Serum**

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<td>2</td>
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</tbody>
</table>

Reference values apply to all ages.


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**Grass Panel # 3, Serum**

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

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

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**GAB1**

**GRB2-Associated Binding Protein 1 (GAB1) Immunostain, Technical Component Only**

**Clinical Information:** GAB1 (growth factor receptor bound protein 2-associated protein 1) is an adapter protein that is involved in growth, transformation, and apoptosis. GAB1 can be used with a panel of immunohistochemical markers in the classification of medulloblastomas into SHH (sonic hedgehog), WNT (wingless-type murine mammary tumor), or non-SHH/WNT subgroups.

**Useful For:** Identification and differentiation of medulloblastomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Greek Fennel, IgE, Serum**

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

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

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

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</tr>
</tbody>
</table>


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**Green Coffee Bean, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to green coffee bean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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</tr>
</tbody>
</table>

Reference values apply to all ages.


**GPEA 82887**

**Green Pea, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to green pea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<tr>
<td>6</td>
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</tbody>
</table>

Reference values apply to all ages.


GPEP 82623

Green Pepper, IgE, Serum

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

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

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

Reference Values:

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<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Green String Bean, IgE, Serum**

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

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

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

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<tr>
<td>6</td>
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<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Grey Alder, IgE, Serum

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

Useful For: Establishing the diagnosis of an allergy to grey alder trees Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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GRHPZ GRHPR Gene, Full Gene Analysis, Varies

Clinical Information: Primary hyperoxaluria type 2 (PH2) is a hereditary disorder of glyoxylate metabolism caused by deficiency of the hepatic enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR). Absence of GRHPR activity results in excess oxalate and usually L-glycerate excreted in the urine leading to nephrolithiasis (kidney stones) and sometimes renal failure. Onset of PH2 is typically in childhood or adolescence with symptoms related to kidney stones. In some cases, kidney failure may be the initial presenting feature. Nephrocalcinosis, as seen by renal ultrasound, is observed less frequently in individuals with PH2 than primary hyperoxaluria type 1 (PH1). End-stage renal disease (ESRD) is also less common and of later onset than PH1; however, once ESRD develops,
oxalate deposition in other organs such as bone, retina, and myocardium can occur. While the exact prevalence and incidence of PH2 are not known, it is thought that PH2 is less common than PH1, which has an estimated prevalence rate of 1 to 3 per million population and an incidence of 0.1 per million/year. Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate in a timed, 24-hour urine collection is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, Urine). In very young children (incapable of performing a timed collection), random urine oxalate to creatinine ratios may be used for determination of oxalate excretion. In patients with reduced kidney function, POXA / Oxalate, Plasma is also recommended. Urinary excretion of oxalate of >1.0 mmol/1.73 m(2)/24 hours is strongly suggestive of, but not diagnostic, for primary hyperoxaluria as there are other forms of inherited hyperoxaluria (PH1 and non-PH1/PH2) and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycerate in the presence of hyperoxaluria is suggestive of PH2. Caution is warranted in interpretation of urine oxalate excretion in patients with reduced kidney function as urine oxalate concentrations may be lower due to reduced glomerular filtration rate. Historically, the diagnosis of PH2 was confirmed by GRHPR enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases. PH2 is inherited as an autosomal recessive disorder caused by mutations in the GRHPR gene, which encodes the enzyme GRHPR. Two common GRHPR mutations have been identified: c.103delG and c.403_404+2delAAGT. These mutations account for about one-third of the mutant alleles described in the Northern European Caucasian population and about 15% in the Asian population. Direct sequencing of the GRHPR gene will identify these 2 mutations as well as other less common or novel mutations associated with PH2.

**Useful For:** Confirming a diagnosis of primary hyperoxaluria type 2 (PH2) Carrier testing for individuals with a family history of PH2 in the absence of known mutations in the family

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

## Group A Streptococcus (Streptococcus pyogenes) Culture, Varies

**Clinical Information:** Streptococcus pyogenes (group A streptococcus) is a common cause of pharyngitis and skin and soft tissue infection. In children, S pyogenes can cause perianal infection. The classic presentation is a well-demarcated rash around the anus with itching, rectal pain, and, occasionally, blood-streaked stools. Untreated, painful defecation, toilet avoidance, and constipation may persist for months, until effective treatment is administered. Anal fissures may ensue. A swab of the affected area may be submitted for S pyogenes culture to confirm the diagnosis. Health care workers may transmit S pyogenes to their patients (eg, in the postsurgical setting) leading to outbreaks of invasive disease. Screening of health care workers or other patients for S pyogenes may be requested by Infection Prevention and Control as part of an investigation of a potential nosocomial case (or cases). Isolates may

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**CGAS**

**62989**

**Group A Streptococcus (Streptococcus pyogenes) Culture, Varies**

**Clinical Information:** Streptococcus pyogenes (group A streptococcus) is a common cause of pharyngitis and skin and soft tissue infection. In children, S pyogenes can cause perianal infection. The classic presentation is a well-demarcated rash around the anus with itching, rectal pain, and, occasionally, blood-streaked stools. Untreated, painful defecation, toilet avoidance, and constipation may persist for months, until effective treatment is administered. Anal fissures may ensue. A swab of the affected area may be submitted for S pyogenes culture to confirm the diagnosis. Health care workers may transmit S pyogenes to their patients (eg, in the postsurgical setting) leading to outbreaks of invasive disease. Screening of health care workers or other patients for S pyogenes may be requested by Infection Prevention and Control as part of an investigation of a potential nosocomial case (or cases). Isolates may
be typed to assess strain relatedness.

**Useful For:** Diagnosis of perianal cellulitis Screening patients and health care workers for Streptococcus pyogenes for the purpose of investigating possible nosocomial transmission

**Interpretation:** Positive cultures are reported out as Streptococcus pyogenes.

**Reference Values:**
Negative

**Clinical References:**

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**CGBS**

**Group B Streptococcus (Streptococcus agalactiae) Culture, Varies**

**Clinical Information:** Streptococcus agalactiae (group B streptococcus) is a cause of morbidity and mortality among infants. Infections occurring within the first week of life are considered early-onset; those occurring in infants greater than 1 week of age are considered late-onset. Maternal vaginal or rectal colonization with S agalactiae is a risk factor for early-onset disease in infants. Ten to 30% of pregnant women are vaginally or rectally colonized with S agalactiae and may transmit the organism to their infant during labor and delivery. The American College of Obstetricians and Gynecologists recommends screening for colonization with S agalactiae at 36 to 37 weeks gestation as a guide for intrapartum antibiotic prophylaxis to decrease the risk of infection with Streptococcus agalactiae in the infant.

**Useful For:** Screening for maternal colonization with Streptococcus agalactiae at 36 to 37 weeks gestation as a guide for intrapartum antibiotic prophylaxis to decrease the risk of infection by S agalactiae (group B streptococcus) in the infant

**Interpretation:** Positive cultures are reported out as Streptococcus agalactiae.

**Reference Values:**
Negative


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**FGRPR**

**Grouper IgE**

**Interpretation:** Class IgE (kU/L)
Comment 0 <0.10 Negative 0/1 0.10 ~/ųęe 0.34
Equivocal/Borderline 1 0.35 ~/ųęe, ~/ųęe 0.69 Low Positive 2 0.70 ~/ųęe, ~/ųęe 3.49 Moderate Positive 3 3.50 ~/ųęe, ~/ųęe 17.49 High Positive 4 17.50 ~/ųęe, ~/ųęe 49.99 Very High Positive 5 50.00 ~/ųęe, ~/ųęe 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

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**GDF15**

**Growth Differentiation Factor 15, Plasma**

**Clinical Information:** Mitochondria perform many important metabolic functions, the most vital being the production of energy in the form of adenosine triphosphate (ATP) through the
electron-transport chain and the oxidative phosphorylation system, which consists of 5 complexes (complex I-V). Each of these complexes consists of 4 to 46 subunits encoded by both nuclear and mitochondrial DNA. Mitochondrial diseases are caused by defects in any of the relevant metabolic pathways and have an estimated prevalence of 1:8,500. Mitochondrial diseases are varied, including mitochondrial DNA deletion syndromes such as Kearns-Sayre syndrome (KSS), mitochondrial depletion syndromes such as those caused by alterations in the TK2 and SUCLA2 or POLG and C10orf2 genes, and mitochondrial point mutation syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), as well as others. The clinical features of mitochondrial diseases vary widely, but they can include lactic acidosis, myopathy, ophthalmoplegia, ptosis, cardiomyopathy, sensorineural hearing loss, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalomyopathy, seizures, and stroke-like episodes. A diagnostic workup for a mitochondrial disorder may demonstrate elevations of the lactate-to-pyruvate ratio (LAA / Lactate, Plasma and PYR / Pyruvic Acid, Blood) and an elevated growth differentiation factor 15 (GDF15) level. GDF15 is a protein of the transforming growth factor beta superfamily. GDF15 is overexpressed in muscle and serum in patients with various types of mitochondrial diseases, including those with mitochondrial deletion, depletion, and point mutation syndromes. Therefore, increased levels of GDF15 can indicate the need for further investigations including molecular studies and muscle biopsy to confirm the presence of a possible neuromuscular mitochondrial disease.

**Useful For:** A circulating biomarker in myopathy-related mitochondrial disease as well as other conditions Investigation of patients suspected of having a mitochondrial myopathy This assay is not suitable for carrier detection.

**Interpretation:** Abnormal results along with clinical findings may be suggestive of mitochondrial disease. Additional workup is indicated.

**Reference Values:**
3 months* and older: < or =750 pg/mL
*This test is not recommended for infants <3 months of age due to the high levels of growth differentiation factor 15 contributed from the placenta during pregnancy.

**Clinical References:**

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**GRH 70444**

**Growth Hormone Immunostain, Technical Component Only**

**Clinical Information:** Growth hormone (GH) is a 21-kD polypeptide hormone that stimulates protein synthesis and may act primarily via the somatomedins. Somatotroph cells produce GH and constitute a high proportion of anterior pituitary cells (50%). GH shows cytoplasmic staining of normal pituitary somatotroph cells and GH adenomas. Globular juxtanuclear staining may be present in some adenomas.

**Useful For:** Aids in the identification of growth hormone adenomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
1. Lea RW, Dawson T, Martinez-Moreno CG, El-Abry N, Harvey S: Growth
HGH 8688

**Growth Hormone, Serum**

**Clinical Information:** The anterior pituitary secretes human growth hormone (hGH) in response to exercise, deep sleep, hypoglycemia, and protein ingestion. hGH stimulates hepatic insulin-like growth factor-1 and mobilizes fatty acids from fat deposits to the liver. Hyposecretion of hGH causes dwarfism in children. Hypersecretion causes gigantism in children or acromegaly in adults. Because hGH levels in normal and diseased populations overlap, hGH suppression and stimulation tests are needed to evaluate conditions of hGH excess and deficiency; random hGH levels are inadequate.

**Useful For:** Diagnosis of acromegaly and assessment of treatment efficacy when interpreted in conjunction with results from glucose suppression test Diagnosis of human growth hormone deficiency when interpreted in conjunction with results from growth hormone stimulation test This test is not intended for use as a screen for acromegaly. This test has limited value in assessing growth hormone secretion in normal children.

**Interpretation:** Acromegaly: For suppression testing, normal subjects have a nadir human growth hormone (hGH) concentration below 0.3 ng/mL after ingestion of a 75-gram glucose dose. Patients with acromegaly fail to show normal suppression. Using the Access ultrasensitive hGH assay, a cutoff of 0.53 ng/mL for nadir hGH was found to most accurately differentiate patients with acromegaly in remission from active disease with a sensitivity of 97% (95% CI, 83%-100%) and a specificity of 100% (95% CI, 82%-100%).(1) Deficiency: A normal response following stimulation tests is a peak hGH concentration above 5 ng/mL in children and above 4 ng/mL in adults. For children, some experts consider hGH values between 5 ng/mL and 8 ng/mL equivocal and only GH peak values greater than 8 ng/mL as truly normal. Low levels, particularly under stimulation, indicate hGH deficiency.

**Reference Values:**

**Adults**
- Males: 0.01-0.97 ng/mL
- Females: 0.01-3.61 ng/mL

Reference intervals have not been formally verified in-house for pediatric and adolescent patients. The published literature indicates that reference intervals for adult, pediatric, and adolescent patients are comparable.

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

**Clinical References:**
Growth Hormone-Releasing Hormone (IR-GH-RH) (Immunoreactive GH-RH)

**Clinical Information:** Growth Hormone Releasing Hormone is a 44 amino acid peptide produced primarily by the hypothalamus. It is a neurohumoral control for adenohypophyseal secretion of Growth Hormone. Other hypothalamic hormones have a stimulatory effect on pituitary hormones, but Growth Hormone Releasing Hormone has no known effect on other pituitary hormones. Somatostatin is the inhibitory counterpart of Growth Hormone Releasing Hormone. Growth Hormone Releasing Hormone has structural similarities with the Secretin-Glucagon family of gastrointestinal hormones. Growth Hormone Releasing Hormone has been isolated from pancreatic islet cells and various cancer tumor cells.

**Reference Values:**
Levels of IR-GH-RH
Baseline ranges: 5 - 18 pg/mL

Guar Gum, IgE, Serum

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Guinea Pig Epithelium, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to guinea pig epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Gum Arabic, IgE, Serum

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35–0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70–3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50–17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5–49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0–99.9</td>
<td>Very Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Very Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FGUMX**

**Gum Carageenan IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**FGUMX**

**Gum Xanthan IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L
Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

**Hackberry (Celtis occidentalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

**Haddock (Melanogrammus aeglefinus) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal 1 0.35 – 0.69 Low Positive 2 0.70 – 3.4 Moderate Positive 3 3.5 – 17.4 High Positive 4 17.5 – 49.9 Very High Positive 5 50.0 – 99.9 Very High Positive 6 >100 Very High Positive

Reference Values:
<0.35 kU/L

**Haemophilus influenzae Type B Antibody, IgG, Serum**

**Clinical Information:** Haemophilus influenzae type B (HIB) is an encapsulated gram-negative cocco-bacillary bacterium that can cause devastating disease in young children including meningitis, bacteremia, cellulitis, epiglottitis, pneumonia, and septic arthritis. One of the great advances in modern medicine has been the development of an effective vaccine against HIB. A patient's immunological response to HIB vaccine can be determined by measuring anti-HIB IgG antibody using this enzyme immunoassay (EIA) technique.

**Useful For:** Assessing a patient's immunological (IgG) response to Haemophilus influenzae type B (HIB) vaccine Assessing immunity against HIB Aiding in the evaluation of immunodeficiency when the patient is tested pre- and postvaccination

**Interpretation:** An anti-Haemophilus influenzae type B (HIB) IgG antibody concentration of 0.15 mg/L is generally accepted as the minimum level for protection at a given time; however, it does not confer long-term protection. A study from Finland suggested that the optimum protective level is 1.0 mg/L postimmunization.(1) Furthermore, studies have shown that the response to HIB vaccine is age-related.

**Reference Values:**
> or =0.15 mg/L
Reference values apply to all ages.

Hairy Cell Leukemia (DBA44) Immunostain, Technical Component Only

**Clinical Information:** Hairy cell leukemia (DBA.44) antibody recognizes an unknown, fixation-resistant antigen that is expressed in normal mantle zone B-cells. It may be expressed in endothelial cells, monocytoid B cells, and scattered immunoblasts as well. It is characteristically expressed in hairy cell leukemia, as well as a subset of marginal zone lymphomas, and may be useful in classification of these lymphomas.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Hake, Fish, IgE, Serum

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Halibut IgG

**Interpretation:**

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

Halibut, IgE, Serum

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

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

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Range</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>
Class IgE kU/L  Interpretation
0              Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6 > or =100  Strongly positive Reference values apply to all ages.


HALO  80339

Haloperidol, Serum

Clinical Information: Haloperidol (Haldol) is a member of the butyrophenone class of neuroleptic drugs used to treat psychotic disorders (eg, schizophrenia). It is also used to control the tics and verbal utterances associated with Tourette syndrome and in the management of intensely hyperexcitable children who fail to respond to other treatment modalities. The daily recommended oral dose for patients with moderate symptoms is 0.5 to 2.0 mg; for patients with severe symptoms, 3 to 5 mg may be used. However, some patients will respond only at significantly higher doses. Haloperidol is metabolized in the liver to reduced haloperidol, its major metabolite.(1,2) Use of haloperidol is associated with significant toxic side effects, the most serious of which include tardive dyskinesia, which can be irreversible, extrapyramidal reactions with Parkinson-like symptoms, and neuroleptic malignant syndrome. Less serious side effects can include hypotension, anticholinergic effects (blurred vision, dry mouth, constipation, urinary retention), and sedation. The risk of developing serious, irreversible side effects seems to increase with increasing cumulative doses over time.(1,3)

Useful For: Optimizing haloperidol dosage Monitoring patient compliance Assessing toxicity

Interpretation: Studies show a strong relationship between dose and serum concentration (4); however, there is a modest relationship of clinical response or risk of developing long-term side effects to either dose or serum concentration. A therapeutic window exists for haloperidol, but some patients may respond to concentrations outside of this range. Patients who respond at serum concentrations between 5 to 16 ng/mL show no additional improvement at concentrations greater than 16 to 20 ng/mL.(3,5) Some patients may respond at concentrations less than 5 ng/mL, and others may require concentrations significantly greater than 20 ng/mL before an adequate response is attained. Because of such inter-individual variation, the serum concentration should only be used as one factor in determining the appropriate dose and must be interpreted in conjunction with the clinical status. Although the metabolite, reduced haloperidol, has minimal pharmacologic activity, evidence has been presented suggesting that an elevated ratio of reduced haloperidol-to-haloperidol (ie, >5) is predictive of a poor clinical response.(3,6) A reduced haloperidol-to-haloperidol ratio <0.5 indicates noncompliance; the metabolite does not accumulate except during steady-state conditions.

Reference Values:
HALOPERIDOL:
5-16 ng/mL

REDUCED HALOPERIDOL:
10-80 ng/mL

Hamster Epithelium, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to hamster epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Hantavirus Antibody (IgG, IgM)

**Interpretation:** This assay detects antibodies against recombinant Hantavirus antigens of both old world and new world Hantavirus types. The immune response to Hantavirus infection is not type-specific, and thus cross-reactivity may occur. All Hantavirus IgM-positive samples from US residents will be sent to a Public Health Laboratory for Sin Nombre Virus (SNV)-specific IgM testing. Samples that are Hantavirus IgG positive but IgM negative will not be subjected to further type-specific testing, since the lack of IgM rules out acute infection.

**Reference Values:**
Reference Range: Negative

Haptoglobin, Serum

**Clinical Information:** Haptoglobin is an immunoglobulin-like plasma protein that binds hemoglobin. The haptoglobin-hemoglobin complex is removed from plasma by macrophages and the hemoglobin is catabolized. When the hemoglobin-binding capacity of haptoglobin is exceeded, hemoglobin passes through the renal glomeruli, resulting in hemoglobinuria. Chronic intravascular hemolysis causes persistently low haptoglobin concentration. Regular strenuous exercise may cause sustained low haptoglobin, presumably from low-grade hemolysis. Low serum haptoglobin may also be due to severe liver disease. Neonatal plasma or serum specimens usually do not contain measurable haptoglobin; adult levels are achieved by 6 months. Increase in plasma haptoglobin concentration occurs as an acute-phase reaction. Levels may appear to be increased in conditions such as burns and nephrotic syndrome. An acute-phase response may be confirmed and monitored by assay of other acute-phase reactants such as alpha-1-antitrypsin and C-reactive protein.

**Useful For:** Confirmation of intravascular hemolysis

**Interpretation:** Absence of plasma haptoglobin may therefore indicate intravascular hemolysis. However, congenital anhaptoglobinemia is common, particularly in African-Americans. For this reason, it may be difficult or impossible to interpret a single measurement of plasma haptoglobin. If the assay value is low, the test should be repeated after 1 to 2 weeks following an acute episode of hemolysis. If all the plasma haptoglobin is removed following an episode of intravascular hemolysis, and if hemolysis ceases, the haptoglobin concentration should return to normal in a week. Low levels of plasma haptoglobin may indicate intravascular hemolysis.

**Reference Values:**
30-200 mg/dL

**Clinical References:**

Hazelnut Component Panel

**Clinical Information:** This assay is used to detect allergen specific-IgE using the ImmunoCAP FEIA method. In vitro allergy testing is the primary testing mode for allergy diagnosis.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE (kU/L)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>0/1</td>
<td>0.10-0.34</td>
</tr>
</tbody>
</table>
Hazelnut Component rCor a 1

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.10 kU/L

Hazelnut-Food, IgE, Serum

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

**Useful For:** Establishing a diagnosis of an allergy to hazelnut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.00-99.9</td>
<td>Strongly positive</td>
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</tbody>
</table>

**HAZ 82670**  
**Hazelnut-Tree, IgE, Serum**  
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to hazelnut-tree  
Defining the allergen responsible for eliciting signs and symptoms  
Identifying allergens:  
- Responsible for allergic disease and/or anaphylactic episode  
- To confirm sensitization prior to beginning immunotherapy  
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**H MUOE 60889**  
**Heavy Metal Occupational Exposure, with Reflex, Random, Urine**  
**Clinical Information:** Arsenic (As), lead (Pb), cadmium (Cd), and mercury (Hg) are well-known
toxins and toxic exposures are characterized by increased urinary excretion of these metals. Arsenic is a naturally occurring element that is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsensobetaine and arsenecholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[+3]/As[III]) and arsenate (As[+5]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsinic acid (MMA) and subsequently dimethylarsinic acid (DMA). People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsensobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated renal damage. The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor.

**Useful For:** Preferred screening test for detection of arsenic, cadmium, mercury and lead due to occupational exposure using random urine specimens

**Interpretation:** Arsenic: Mayo Clinic uses the American Conference of Governmental Industrial Hygienists (ACGIH) biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated arsenic forms) or the relatively nontoxic organic forms (eg, arsensobetaine and arsenecholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary As[III] and As[V] concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health. Cadmium: In chronic cadmium exposure, the kidneys are the primary target organ. Urine concentrations of cadmium can be useful to assess long-term exposure and determine cadmium body burden. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration (OSHA) cadmium standard is below 3.0 mcg/g creatine and the BEI is 5 mcg/g creatine. Mercury: It had always been thought that urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) Lead: Measurements of urinary lead levels have been used...
to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure.(3,4) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(5,6)

**Reference Values:**

**ARSENIC:**

Biological Exposure Indices (BEI): <35 mcg/L at end of work week

**CADMIUM:**

BEI: <5.0 mcg/g creatinine

**MERCURY:**

BEI: <35 mcg/g creatinine

**LEAD:**

BEI: <150 mcg/g creatinine

**Clinical References:**

and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Arsenic toxicity affects a number of organ systems. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated renal damage. The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor.

**Useful For:** Preferred screening test for detection of arsenic, cadmium, mercury, and lead in random urine specimens

**Interpretation:** Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (e.g. inorganic and methylated forms) or the relatively nontoxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health. Cadmium: Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration (OSHA) cadmium standard is below 3.0 mcg/g creatine and the biological exposure index is 5 mcg/g creatinine. Mercury: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. It had always been thought that urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%), consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood. Lead: Measurements of urinary lead levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure. Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.

**Reference Values:**

**ARSENIC/CREATININE:**
- 0-17 years: not established
- > or =18 years: <24 mcg/g creatinine

**CADMIUM/CREATININE:**
- 0-17 years: not established
- > or =18 years: <0.6 mcg/g creatinine
MERCURY/CREATININE:
0-17 years: not established
> or =18 years: <2 mcg/g creatinine

LEAD/CREATININE:
0-17 years: not established
> or =18 years: <2 mcg/g creatinine

Clinical References:

Heavy Metals Screen with Demographics, Blood

Clinical Information: Arsenic: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(5+), also denoted as As(V), the more toxic As(3+), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(3+) is oxidized to As(5+) and then methylated to MMA and DMA. As a result of these detoxification steps, As(3+) and As(5+) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because of its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea,
epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur. Lead: Lead is a heavy metal commonly found in man’s environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978 but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of unleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke. Mercury: Mercury (Hg) is essentially nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(2+), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg ([CH3Hg][+]), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Not Toxic ~ Hg(0) < Hg(2+) << [CH3Hg][+] -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents such as chlorine. Hg(0) can be bioconverted to both Hg(2+) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(2+), [CH3Hg][+], and (CH3)(2+)Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in a rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(2+) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein—a stereoisomeric change—with subsequent loss of the unique activity associated with that protein. Because Hg(2+) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as [CH3Hg][+], are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial flora present in the mouth converts a fraction of this to Hg(2+) and [CH3Hg][+], which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other
source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain less than 0.3 mcg/g of mercury, but some game fish contain more than 2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is below 50 mcg/day.

Useful For: Detecting exposure to arsenic, lead, cadmium, and mercury

Interpretation: Arsenic: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of <6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen. Lead: The 95th percentile of the Gaussian distribution of whole blood lead concentration in a population of unexposed adults is <6.0 mcg/dL. For pediatric patients, there may be an association with blood lead values of 5.0 to 9.9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is >25.0 mcg/dL in children or >45.0 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result >60.0 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels >50.0 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is <40 mcg/dL. New York State has mandated inclusion of the following statement in reports for children under the age of 6 with blood lead in the range of 5.0 to 9.9 mcg/dL: "Blood lead levels in the range of 5.0-9.9 mcg/dL have been associated with adverse health effects in children aged 6 years and younger." Cadmium: Normal blood cadmium is <5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL. Mercury: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually <10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is >50 ng/mL if exposure is due to alkyl Hg, or >200 ng/mL if exposure is due to Hg(+2).

Reference Values:

**ARSENIC**
<13 ng/mL
Reference values apply to all ages.

**LEAD**
All ages: <5.0 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

**CADMIUM**
<5.0 ng/mL
Reference values apply to all ages.

**MERCURY**
<10 ng/mL
Reference values apply to all ages.

excretion rate before AND after chelation therapy has been used as an indicator of lead exposure. Lead: Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead from dietary consumption of fish/seafood.(2) For additional information, see HG / Mercury, Blood to demethylation processes in the human body, a certain proportion of urinary mercury can originate can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a excretion in the urine and the clinical symptoms is considered poor. It had always been thought that some patients exposed to cadmium. Mercury: The correlation between the levels of mercury (Hg) in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Clinical Information: Arsenic: Arsenic is a naturally occurring element that is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenucholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+)/As[III]) and arsenate (As[5+)/As[V]). Inorganic As(V) is readily reduced to inorganic As(III) which is then primarily broken down to less toxic methylated metabolites monomethylarsonic acid (MMA) and subsequently dimethylarsinic acid (DMA). People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and if not disposed of properly may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Arsenic and if not disposed of properly may get into the surrounding water, air, or soil. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. 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Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in some patients exposed to cadmium. Mercury: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. It had always been thought that urate was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) For additional information, see HG / Mercury, Blood Lead: Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before AND after chelation therapy has been used as an indicator of lead exposure.
However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." Blood lead is the best clinical correlation of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

**Useful For:** Detecting arsenic, cadmium, mercury, and lead exposure and toxicity using 24-hour urine specimen

**Interpretation:** Arsenic: Mayo Clinic uses the American Conference of Governmental Industrial Hygienists (ACGIH) biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (e.g. inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (e.g. inorganic and methylated arsenic forms) or the relatively non-toxic organic forms (e.g. arsenobetaine and arslenocholine). The inorganic toxic forms of arsenic (e.g. As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. After a seafood meal (seafood generally contains the nontoxic, organic form of arsenic (e.g., arsenobetaine), the urine output of arsenic may increase to over 300 mcg/specimen for a day, after which it will decline. This test can determine if the patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health. Cadmium: In chronic cadmium exposure, the kidneys are the primary target organ. Urine concentrations of cadmium can be useful to assess long-term exposure and determine cadmium body burden. Collection of urine over 24 hours minimizes fluctuations of observed cadmium concentrations in random urine samples. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration (OSHA) cadmium standard is <3.0 mcg/g creatine and the BEI is 5 mcg/g creatinine. Mercury: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard). Lead: Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure.(3,4) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(5,6)

**Reference Values:**

**ARSENIC:**
- 0-17 years: not established
- \( \geq 18 \) years: <35 mcg/24 hour

**CADMIUM:**
- 0-17 years: not established
- \( \geq 18 \) years: <0.7 mcg/24 hour

**MERCURY:**
- 0-17 years: not established
- \( \geq 18 \) years: <2 mcg/24 hour
- Toxic concentration: >50 mcg/24 hour

The concentration at which toxicity is expressed is widely variable between patients. 50 mcg/24 hour is the lowest concentration at which toxicity is usually apparent.

**LEAD:**
- 0-17 years: not established
Clinical References: 

Heavy Metals, Hair

Clinical Information: Arsenic Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, "trapping" the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hairs are used to document long-term (6 months-1 year) exposure. Mercury Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If the hair can be segregated by length, such an exercise can be useful in identifying the time of exposure. Lead Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

Useful For: Detection of nonacute arsenic, mercury, and lead exposure using hair specimens

Interpretation: Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level
represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc.

ARSENIC Hair arsenic levels above 1.00 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure, which was the cause of death. MERCURY Normally, hair contains less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury may have occurred. LEAD Normal hair lead content is below 4.0 mcg/g. While hair lead content above 10.0 mcg/g may indicate significant lead exposure, hair is also subject to potential external contamination with environmental lead and contaminants in artificial hair treatments (eg, dyeing, bleaching, or permanents). Ultimately, the hair lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:

**ARSENIC**
- 0-15 years: not established
- > or =16 years: <1.0 mcg/g of hair

**LEAD**
- <4.0 mcg/g of hair
- Reference values apply to all ages.

**MERCURY**
- 0-15 years: not established
- > or =16 years: <1.0 mcg/g of hair

Clinical References:

Heavy Metals, Nails

**Clinical Information:** Arsenic Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mee's' lines, may appear in the fingernails. Mercury Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms. If the nails can be segregated by length, such an exercise may be useful in identifying the time of exposure. Lead Nail analysis of lead can be used to corroborate blood analysis.

**Useful For:** Detection of nonacute arsenic, mercury, and lead exposure

**Interpretation:** Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. ARSENIC Nail arsenic above 1.0 mcg/g dry weight may indicate
excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure, which was the cause of death. MERCURY Normally, nails contain less than 1 mcg/g of mercury; any amount above this indicates that exposure to more than normal amounts of mercury may have occurred. LEAD Normally, the nail lead content is below 4.0 mcg/g. While nail lead content above 10.0 mcg/g may indicate significant lead exposure, nails are also subject to potential external contamination with environmental lead. Ultimately, the nail lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:
ARSENIC
0-15 years: not established
> or =16 years: <1.0 mcg/g of nails

LEAD
<4.0 mcg/g of nails
Reference values apply to all ages.

MERCURY
0-15 years: not established
> or =16 years: <1.0 mcg/g of nails


HPYL 70466
Helicobacter pylori (H pylori) Immunostain, Technical Component Only
 Clinical Information: Helicobacter pylori is a bacterium that frequently infects the stomach, colonizing the gastric pits. H pylori infection is associated with the development of gastroduodenal ulcers and gastric mucosa-associated lymphoid tissue (MALT) lymphomas.

Useful For: Aiding in the identification of Helicobacter pylori infection

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Helicobacter pylori Antigen, Feces**

**Clinical Information:** Helicobacter pylori is well recognized as the cause of chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia. Currently accepted methods for the diagnosis of Helicobacter pylori infection include serologic tests, the urea breath test (UBT), and culture or histologic examination or direct urease testing (CLO test) of biopsy specimens obtained at the time of gastroduodenoscopy (ENDO). Each of these tests has its drawbacks, including lack of specificity (serology) or high cost, complexity, and inconvenience for the patient (UBT and END0). See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

**Useful For:** As an aid in the diagnosis of Helicobacter pylori Monitoring the eradication of Helicobacter pylori after therapy (in most situations, confirmation of eradication is not mandatory) The utility of this test in asymptomatic individuals is not known, but testing for Helicobacter pylori in such individuals is not generally recommended.

**Interpretation:** Positive results indicate the presence of Helicobacter pylori antigen in the stool. Negative results indicate the absence of detectable antigen but does not eliminate the possibility of infection due to Helicobacter pylori.

**Reference Values:**
Negative

**Clinical References:**

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**Helicobacter pylori Breath Test**

**Clinical Information:** The causal relationship between the urease-producing bacterium, Helicobacter pylori, and chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia is well established. Conventional methods for the diagnosis of active H pylori infection include evaluation of biopsied gastric tissue by histopathology and culture. Less invasive assays include testing for the presence of H pylori by polymerase chain reaction (PCR) in stool specimens and detection of H pylori urease production by the urea breath test (UBT). Serologic testing for the presence of IgM/IgG/IgA-class antibodies to H pylori is also performed; however, this is not recommended by either the American College of Gastroenterologists nor the American Gastroenterological Association (AGA) as an accurate marker for active disease. These serologic markers can remain elevated despite resolution of active disease and may lead to misdiagnosis and inappropriate treatment. Recommendations for use of the (13)C-UBT (Meretek) were recently provided by the Digestive Health Initiative, a joint committee assembled with representatives from the AGA, the American Society for Gastrointestinal Endoscopy (ASGE), and the American Association for the Study of Liver Diseases (AASLD).(1) These recommendations include the following statements: "When endoscopy is not clinically indicated, the primary diagnosis of H pylori infection can be made serologically or with the UBT. When endoscopy is clinically indicated, the primary diagnosis should be established by biopsy urease testing and/or histology. Available evidence suggests that confirmation of H pylori eradication is not mandatory in most situations because of costs associated with testing. However, for selected patients with complicated ulcer disease, low-grade gastric mucosa-associated lymphoid tissue lymphoma, and following resection of early gastric cancer, it is appropriate to confirm eradication. In other situations, the decision to confirm H pylori eradication should be made on a case-by-case basis." This consensus group further specifies that there is no indication to test asymptomatic people and that testing for H pylori is only recommended if treatment is planned. The (13)C-UBT is a highly sensitive and specific noninvasive, nonradioactive test for diagnosing H pylori infection prior to antimicrobial treatment and for assessing whether the organism has been successfully eradicated following antimicrobial therapy. In 2 recent large prospective studies, the (13)C-UBT was shown to be as, or more, sensitive and specific for diagnosing H pylori active infection than culture, stain, rapid urease testing of...
biopsy tissue, or serology. When the test is used to assess eradication, it should be performed 4 to 6 weeks after completion of antimicrobial treatment. See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

**Useful For:** Diagnostic testing for Helicobacter pylori infection in patients suspected to have active H pylori infection Monitoring response to therapy This test is not appropriate for asymptomatic people.

**Interpretation:** The Helicobacter pylori urea breath test can detect very low levels of H pylori and, by assessing the entire gastric mucosa, avoids the risk of sampling errors inherent in biopsy-based methods. In the absence of gastric H pylori, the (13)C-urea does not produce (13)CO2 in the stomach. A negative result does not rule out the possibility of H pylori infection. If clinical signs are suggestive of H pylori infection, retest with a new specimen or by using an alternative method. A false-positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as Helicobacter heilmannii. A false-positive test could occur in patients who have achlorhydria.

**Reference Values:**
Negative Reference values apply to all ages.

**Clinical References:**

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**Helicobacter pylori Culture with Antimicrobial Susceptibilities, Varies**

**Clinical Information:** Helicobacter pylori is a spiral-shaped Gram-negative bacterium that may cause chronic gastritis, peptic ulcer disease, or gastric neoplasia. In adults of industrialized countries, an estimated 0.5% of the susceptible population becomes infected each year, although the incidence has been decreasing over time. The organism may asymptotically colonize humans. In suspected H pylori-associated disease, the H pylori with clarithromycin resistance prediction polymerase chain reaction (PCR) test or urea breath test is recommended for patients less than 60 years old without alarming signs and symptoms (see Helicobacter pylori Diagnostic Algorithm in Special Instructions). If clarithromycin resistance is predicted by the PCR test, endoscopy with biopsy should be considered for H pylori culture with antimicrobial susceptibility testing. For those greater than or equal to 60 years old or who have alarming signs and symptoms, endoscopy with biopsy is recommended, with consideration for H pylori culture with antimicrobial susceptibility testing on the gastric biopsy. If patients fail to respond to treatment, endoscopy with biopsy should be considered for H pylori culture with antimicrobial susceptibility testing. The Clinical and Laboratory Standards Institute (CLSI) recommends agar dilution for H pylori antimicrobial susceptibility testing. Amoxicillin, clarithromycin, levofloxacin, metronidazole, and tetracycline are routinely tested. CLSI has defined interpretive categories for clarithromycin. The antimicrobials for which the European Committee on Antimicrobial Susceptibility Testing (EUCAST) defines interpretive categories include amoxicillin, clarithromycin, levofloxacin, metronidazole, and tetracycline.

**Useful For:** Recovery of Helicobacter pylori from gastric specimens for antimicrobial susceptibility testing of the organism (amoxicillin, clarithromycin, levofloxacin, metronidazole, and tetracycline are routinely tested)

**Interpretation:** A positive result provides definitive evidence of the presence of Helicobacter pylori. Organisms may be detected in asymptomatic (colonized) individuals. False-negative culture results may occur since the organism may die between biopsy collection and laboratory culture.

**Reference Values:**
No growth after 7 days
Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL and as susceptible, intermediate, or resistant according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

Susceptible:
A category defined by a breakpoint that implies that isolates with an MIC at or below or a zone diameter at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

Intermediate:
A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and/or for which response rates may be lower than for susceptible isolates.
Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant:
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies. (Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing, 30th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2021)

these alterations was found in 97% of clarithromycin resistant H pylori isolates studied.

**Useful For:** Aiding in the diagnosis of Helicobacter pylori infection and prediction of clarithromycin resistance or susceptibility directly from stool

**Interpretation:** A detected result indicates the presence of Helicobacter pylori 23S ribosomal RNA gene; also indicated is whether or not one of the 3 most common 23S ribosomal RNA gene single nucleotide variations (A2143G, A2142G, and A2142C) associated with clarithromycin resistance is detected. A not detected result for H pylori indicates the absence of detectable H pylori DNA, but does not negate the presence of the organism and may occur due to inhibition of the polymerase chain reaction (PCR), sequence variability underlying primers or probes, or the presence of H pylori DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**Helicobacter pylori with Clarithromycin Resistance Prediction, Molecular Detection, PCR, Varies**

**Clinical Information:** Helicobacter pylori is the main cause of peptic ulcer disease and, when left untreated, a risk factor for gastric cancer. Traditionally, H pylori diagnosis has included non-invasive tests (eg, urea breath test, fecal antigen test) or invasive tests (eg, gastric biopsy). Antimicrobial resistance in H pylori is poorly studied but is rising, challenging its treatment. In 2012, an international clinical consortium study group recommended monitoring of clarithromycin resistance rates and ceasing its use at a threshold range of 15% to 20%.(1) Local monitoring has been practically impossible as not all patients undergo invasive testing, which yields a culture isolate that can be subjected to susceptibility testing. Even if invasive testing is performed, the organism can be difficult to isolate in culture and is highly fastidious once isolated, oftentimes not being amenable to phenotypic susceptibility testing. Further, there are only a handful of specialized clinical microbiology laboratories that perform H pylori susceptibility testing. In an internal study of local and referred isolates published in 2016, clarithromycin resistance was observed to be most commonly due to A2143G (70/88 isolates, 79.6%), followed by A2142G (12/88 isolates, 13.6%) and A2142C (3/88 isolates, 3.4%) alterations in the 23S ribosomal RNA gene.(2) Overall, one of these alterations was found in 97% of clarithromycin-resistant H pylori isolates studied.

**Useful For:** Assessing pure isolates of Helicobacter pylori to predict clarithromycin resistance or susceptibility

**Interpretation:** A detected result indicates the presence of Helicobacter pylori 23S ribosomal RNA gene; the presence or absence of the 3 most common 23S ribosomal RNA gene single nucleotide variations (A2143G, A2142G, and A2142C) is reported. A not detected result indicates the absence of detectable H pylori DNA.

**Reference Values:**
Not applicable

**Clinical References:**

HELM

82749

Helminthosporium halodes, IgE, Serum

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

Useful For: Establishing a diagnosis of an allergy to Helminthosporium halodes Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

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<td>1</td>
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<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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FHSSE

57532

Helminthosporium sativum/Drecshlera IgE

Interpretation: Class IgG (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive
**Hematologic Disorders, Chromosome Hold, Varies**

**Clinical Information:** Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, chromosome analysis may not be necessary. Depending on the diagnosis, fluorescence in situ hybridization (FISH) assays may also be more informative.

**Useful For:** Holding the bone marrow or peripheral blood specimen in the laboratory but delaying chromosome analysis while preliminary morphologic assessment is in process

**Interpretation:** If notified by the client, this test may be canceled and a processing fee assessed. If no notification to cancel testing is received, this test will be reported as "reflexed for chromosome analysis" and depending on the specimen received, CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow or CHRHB / Chromosome Analysis, Hematologic Disorders, Blood will be performed and an interpretive report provided.

**Reference Values:**
Not applicable

**Clinical References:**

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**Hematologic Disorders, DNA and RNA Extract and Hold, Varies**

**Clinical Information:** It is frequently useful to obtain nucleic acid from clinical samples containing a hematopoietic neoplasm at the time of diagnosis, so that appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acid on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

**Useful For:** Reserving nucleic acid on any specimen for which molecular analysis requiring DNA or RNA may be necessary at a future date, ensuring that adequate material for testing is available

**Interpretation:** A report of "Performed" will be sent and a $75 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

**Reference Values:**
Not applicable

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**Hematologic Disorders, DNA Extract and Hold, Varies**

**Clinical Information:** It is frequently useful to obtain nucleic acid from clinical samples containing a hematopoietic neoplasm at the time of diagnosis, so that appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute
myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acid on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

**Useful For:** Reserving nucleic acid on any specimen for which molecular analysis requiring DNA may be necessary at a future date, ensuring that adequate material for testing is available

**Interpretation:** A report of "Performed" will be sent and a $50 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

**Reference Values:**
Not applicable

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**HOLD**

35847

**Hematologic Disorders, Fluorescence In Situ Hybridization (FISH) Hold, Varies**

**Clinical Information:** Fluorescence in situ hybridization (FISH) analysis using gene-specific probes is a useful methodology to detect common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, FISH analysis may not be necessary. Depending on the diagnosis, conventional chromosome analysis may also be more informative.

**Useful For:** Processing the bone marrow or peripheral blood specimen but delaying fluorescence in situ hybridization (FISH) analysis while preliminary morphologic assessment is in process

**Interpretation:** If notified by the client, this test may be canceled and a processing fee will be assessed. If no notification to proceed with testing is received, this test will be reported as "canceled."

**Reference Values:**
Not applicable

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**HLLFH**

34854

**Hematologic Disorders, Leukemia/Lymphoma; Flow Hold, Varies**

**Clinical Information:** Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

**Useful For:** Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytotoxic evidence of differentiation Recognizing monoclonal plasma cells

**Interpretation:** Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.
Reference Values:
When performed, an interpretive report will be provided.
This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist.


P53CA
62402
Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9, Varies

Clinical Information: Patients with chronic lymphocytic leukemia (CLL) have variable disease course influenced by a series of tumor biologic factors. The presence of chromosomal 17p- or a TP53 gene variant confers a very poor prognosis to a subset of CLL patients, both at time of initial diagnosis, as well as at disease progression, or in the setting of therapeutic resistance. TP53 gene variant status in CLL has emerged as the single most predictive tumor genetic abnormality associated with adverse outcome and poor response to standard immunochemotherapy; however, patients can be managed with alternative therapeutic options. Although the prognostic relevance of an acquired TP53 gene variant is best studied for CLL, similar findings are also reported for other hematologic malignancies including low-grade B-cell lymphoma, diffuse large B-cell lymphoma, and some types of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Therefore, while this test has been developed to be primarily focused on high-risk CLL patients, TP53 gene sequencing analysis can also be performed in additional neoplasms, as clinically indicated.

Useful For: Evaluating chronic lymphocytic leukemia patients at diagnosis or during disease course for the presence of TP53 gene variants indicating high risk of disease progression and adverse outcomes. This test is not intended for the evaluation of patients suspected of having an inherited or germline TP53 cancer syndrome (e.g., Li Fraumeni syndrome).

Interpretation: Results are reported in standard nomenclature according to the most recent Human Genome Variation Society (HGVS) recommendations and an interpretive comment regarding the nature of the sequence variant (e.g., known deleterious, suspected deleterious, synonymous change) will be included to complete the clinical report.

Reference Values:
Genetic variants present or absent as compared to a reference sequence of the normal TP53 gene

Hemochromatosis HFE Gene Analysis, Blood

**Clinical Information:** Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism with a carrier frequency of approximately 1 in 10 individuals of northern European ancestry. The disease is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues. Iron overload can cause hepatic cirrhosis, hepatocellular carcinoma, diabetes mellitus, arthropathy, and cardiomyopathy. Such complications can generally be prevented by phlebotomy, and patients have a normal life expectancy if treated before organ damage occurs. For individuals with clinical symptoms consistent with HH or biochemical evidence of iron overload, an HH diagnosis is typically based on the results of transferrin-iron saturation and serum ferritin concentration. Molecular testing can be done to confirm the diagnosis. The majority of HH patients have mutations in the HFE gene. Clinically significant iron overload also can occur in the absence of known HFE mutations, so a negative HFE test does not exclude a diagnosis of iron overload or hemochromatosis. The most common mutation in the HFE gene is C282Y (exon 4, 845G->A). Homozygosity for the C282Y mutation is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of individuals affected with HH are heterozygous for this mutation. These frequencies show variability among different populations, with the highest frequency observed in individuals of northern European ancestry. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical end points (such as diabetes mellitus, hepatic cirrhosis, and cardiomyopathy) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms. The H63D (exon 2, 187C->G) mutation is associated with HH, but the actual clinical effects of this mutation are uncertain. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of additional modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations. Approximately 1% to 2% of individuals with this genotype will develop clinical evidence of iron overload. While individuals with this genotype may have increased iron indices, most will not develop clinical disease without comorbid factors (steatosis, diabetes, or excess alcohol consumption). The clinical significance of a third HFE mutation, S65C (exon 2, 193A->T), appears to be minimal. This rare variant displays a very low penetrance. Compound heterozygosity for C282Y and S65C may confer a low risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type or H63D alleles do not seem to be at an increased risk for HH. The S65C mutation is only reported when it is part of the C282Y/S65C genotype. See Hereditary Hemochromatosis Algorithm in Special Instructions.

**Useful For:** Establishing or confirming the clinical diagnosis of hereditary hemochromatosis (HH) in adults HFE genetic testing is NOT recommended for population screening Testing of individuals with increased transferrin-iron saturation in serum and serum ferritin With appropriate genetic counseling, predictive testing of individuals who have a family history of HH

**Interpretation:** An interpretive report will be provided. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

**Reference Values:** An interpretative report will be provided.


800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Hemoglobin (Hb) Immunostain, Technical Component Only**

**Clinical Information:** This immunostain uses antibodies to hemoglobin that stain red blood cells and red blood cell precursors in bone marrow and in other sites in a diffuse cytoplasmic staining pattern. This stain may be useful in the diagnosis of erythroleukemia or myelodysplastic neoplasms.

**Useful For:** Identification of red blood cells and red blood cell precursors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Hemoglobin A1c, Blood**

**Clinical Information:** Diabetes mellitus is a chronic disorder associated with disturbances in carbohydrate, fat, and protein metabolism characterized by hyperglycemia. It is one of the most prevalent diseases, affecting approximately 24 million individuals in the United States. Long-term treatment of the disease emphasizes control of blood glucose levels to prevent the acute complications of ketosis and hyperglycemia. In addition, long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease can be minimized if blood glucose levels are effectively controlled. Hemoglobin A1c (HbA1c) is a result of the nonenzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The attachment of the hexose molecule occurs continually over the entire life span of the erythrocyte and is dependent on blood glucose concentration and the duration of exposure of the erythrocyte to blood glucose. Therefore, the HbA1c level reflects the mean glucose concentration over the previous period (approximately 8-12 weeks, depending on the individual) and provides a much better indication of long-term glycemic control than blood and urinary glucose determinations. Diabetic patients with very high blood concentrations of glucose have from 2 to 3 times more HbA1c than normal individuals. A Diagnosis of diabetes includes 1 of the following: -Fasting plasma glucose of 126 mg/dL or greater -Symptoms of hyperglycemia and random plasma glucose of 200 mg/dL or greater -Two-hour glucose of 200 mg/dL or greater during oral glucose tolerance test unless there is unequivocal hyperglycemia, confirmatory testing should be repeated on a different day The American Diabetes Association (ADA), International Expert Committee (IEC), and the World Health Organization (WHO) recommend the use of HbA1c to diagnose diabetes, using a threshold of 6.5%. The threshold is based upon sensitivity and specificity data from several studies. Advantages to using HbA1c for diagnosis include: -Provides an assessment of chronic hyperglycemia -Assay standardization efforts from the National Glycohemoglobin Standardization Program (NGSP) have been largely successful and the accuracy of HbA1c is closely monitored by manufacturers and laboratories -No fasting is necessary -Intraindividual variability is very low (<2% variation) -A single test could be used for both diagnosing and monitoring diabetes When using HbA1c to diagnose diabetes, an elevated HbA1c should be confirmed with a repeat measurement, except in those individuals who are symptomatic with a plasma
glucose concentration above 200 mg/dL. Patients who have an HbA1c between 5.7 and 6.4 are considered at increased risk for developing diabetes in the future. (The terms prediabetes, impaired fasting glucose, and impaired glucose tolerance will eventually be phased out by the ADA to eliminate confusion.) The ADA recommends measurement of HbA1c (typically 3-4 times per year for type 1 and poorly controlled type 2 diabetic patients, and 2 times per year for well-controlled type 2 diabetic patients) to determine whether a patient's metabolic control has remained continuously within the target range.

**Useful For:** Evaluating the long-term control of blood glucose concentrations in patients with diabetes Diagnosing diabetes Identifying patients at increased risk for diabetes (prediabetes) This assay is not useful in determining day-to-day glucose control and should not be used to replace daily home testing of blood glucose.

**Interpretation:**
- **Diagnosing diabetes:** American Diabetes Association (ADA) - Hemoglobin A1c (HbA1c): > or =6.5%
- **Therapeutic goals for glycemic control (ADA):**
  - Adults: Minimize the risk of complications of diabetes.
  - Goal of therapy: < 7.0% HbA1c
  - Action suggested: > 8.0% HbA1c
  - Pediatric patients:
    - Toddlers and preschoolers: < 8.5%
    - School age (6-12 years): < 8%
    - Adolescents and young adults (13-19 years): < 7.5%

The ADA recommendations for clinical practice suggest maintaining a HbA1c value closer to normal yields improved microvascular outcomes for diabetics. Target goals of less than 7% may be beneficial in patients such as those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. However, in patients with significant complications of diabetes, limited life expectancy, or extensive comorbid conditions, targeting a less than 7% goal may not be appropriate. Since the HbA1c assay reflects long-term fluctuations in blood glucose concentration, a patient with diabetes who has who has been under good control in recent months may have a high concentration of HbA1c. The converse is true for a patient with diabetes previously under good control who is now poorly controlled. HbA1c results less than 4.0% are reported with the comment: "Falsely low HbA1c results may be observed in patients with clinical conditions that shorten erythrocyte life span or decrease mean erythrocyte age. HbA1c may not accurately reflect glycemic control when clinical conditions that affect erythrocyte survival are present. Fructosamine may be used as an alternate measurement of glycemic control."

**Reference Values:**
- **4.0-5.6%**
  - <18 years: Hemoglobin A1c criteria for diagnosing diabetes have not been established for patients who are <18 years of age.
  - > or =18 years: Increased risk for diabetes (prediabetes): 5.7-6.4%
  - Diabetes: > or =6.5%

Interpretive information based on Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association.

**Clinical References:**

**Hemoglobin Electrophoresis Evaluation, Blood**

**Clinical Information:** A large number of variants of hemoglobin (Hb) have been recognized. Although many do not result in clinical or hematologic effects, clinical symptoms that can be associated with Hb disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis/polycythemia, cyanosis/hypoxia, anemia (chronic, compensated or episodic), and increased methemoglobin or sulfhemoglobin results (M-hemoglobins). For many common Hb variants (e.g. Hb S, Hb C, Hb D and...
Hb E, among many others), protein studies will be sufficient for definitive identification. However, some Hb conditions may be difficult to identify by protein methods alone and may require molecular methods for confirmation. Hb disorders commonly occur as compound disorders (2 or more genetic variants) that can have complex interactions and variable phenotypes. In these situations molecular testing may be necessary for accurate classification. It is important to note that although powerful as an adjunct for a complete and accurate diagnosis, molecular methods without protein data can give incomplete and possibly misleading information due to limitations of the methods. Accurate classification of hemoglobin disorders and interpretation of genetic data requires the incorporation of protein analysis results. This profile is well-suited for the classification of hemoglobin disorders. Mayo Clinic Laboratories receives specimens from a wide geographic area and nearly one-half of all specimens tested exhibit abnormalities. The most common abnormality is an increase in Hb A2 to about 4% to 8%, which indicates beta-thalassemia minor when present in the correct clinical context. A wide variety of other hemoglobinopathies are also frequently encountered. Ranked in order of relative frequency, these are: Hb S (sickle cell disease and trait), C, E, Lepore, G-Philadelphia, Hb H disease, D-Los Angeles, Koln, Constant Spring, O-Arab. Other variants associated with hemolysis, erythrocytosis/polycythemia, microcytosis, cyanosis/hypoxia are routinely identified; however, some will not be detected by routine screening methods and require communication of clinical findings to prompt indicated reflex testing options. Alpha-thalassemia genetic variants are very common in the United States, occurring in approximately 30% of African Americans and accounting for the frequent occurrence of microcytosis in persons of this ethnic group. Some alpha-thalassemia conditions (e.g. Hb H, Barts) can be identified in the hemoglobin electrophoresis protocol, although Hb Constant Spring may or may not be evident by protein methods alone dependent upon the percentage present. It is important to note, alpha-thalassemias that are from only 1 or 2 alpha-globin gene deletions are not recognized by protein studies alone and alpha gene deletion and duplication testing is required.

**Useful For:** Diagnosis and classification of hemoglobin disorders, including thalassemias and hemoglobin variants

**Interpretation:** The hemoglobin (Hb) fractions, including Hb variants are identified and quantitated. An interpretive report that summarizes all testing, including the significance of the findings, is issued.

**Reference Values:**

**HEMOGLOBIN A**
- 1-30 days: 5.9-77.2%
- 1-2 months: 7.9-92.4%
- 3-5 months: 54.7-97.1%
- 6-8 months: 80.0-98.0%
- 9-12 months: 86.2-98.0%
- 13-17 months: 88.8-98.0%
- 18-23 months: 90.4-98.0%
- > or =24 months: 95.8-98.0%

**HEMOGLOBIN A2**
- 1-30 days: 0.0-2.1%
- 1-2 months: 0.0-2.6%
- 3-5 months: 1.3-3.1%
- > or =6 months: 2.0-3.3%

**HEMOGLOBIN F**
- 1-30 days: 22.8-92.0%
- 1-2 months: 7.6-89.8%
- 3-5 months: 1.6-42.2%
- 6-8 months: 0.0-16.7%
- 9-12 months: 0.0-10.5%
- 13-17 months: 0.0-7.9%
- 18-23 months: 0.0-6.3%
- > or =24 months: 0.0-0.9%

**VARIANT 1**
HBELI

608088

Hemoglobin Electrophoresis Interpretation

Clinical Information: A large number of variants of hemoglobin (Hb) have been recognized. Although many do not result in clinical or hematologic effects, clinical symptoms that can be associated with Hb disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis/polycythemia, cyanosis/hypoxia, anemia (chronic, compensated or episodic), and increased methemoglobin or sulfhemoglobin results (M-Hb). For many common Hb variants (eg, Hb S, Hb C, Hb D and Hb E, among many others), protein studies will be sufficient for definitive identification. However, some Hb conditions may be difficult to identify by protein methods alone and may require molecular methods for confirmation. Hb disorders commonly occur as compound disorders (2 or more genetic variants) that can have complex interactions and variable phenotypes. In these situations molecular testing may be necessary for accurate classification. It is important to note that although powerful as an adjunct for a complete and accurate diagnosis, molecular methods without protein data can give incomplete and possibly misleading information due to limitations of the methods. Accurate classification of Hb disorders and interpretation of genetic data requires the incorporation of protein analysis results. This profile is well-suited for the classification of Hb disorders. Mayo Clinic Laboratories receives specimens from a wide geographic area and nearly one-half of all specimens tested exhibit abnormalities. The most common abnormality is an increase in Hb A2 to about 4% to 8%, which indicates beta-thalassemia minor when present in the correct clinical context. A wide variety of other hemoglobinopathies are also frequently encountered. Ranked in order of relative frequency, these are: Hb S (sickle cell disease and trait), C, E, Lepore, G-Philadelphia, Hb H disease, D-Los Angeles, Koln, Constant Spring, O-Arab. Other variants associated with hemolysis, erythrocytosis/polycythemia, microcytosis, cyanosis/hypoxia are routinely identified; however, some will not be detected by routine screening methods and require communication of clinical findings to prompt indicated reflex testing options. Alpha-thalassemia genetic variants are very common in the United States, occurring in approximately 30% of African Americans and accounting for the frequent occurrence of microcytosis in persons of this ethnic group. Some alpha-thalassemia conditions (eg, Hb H, Barts) can be identified in the Hb electrophoresis protocol, although Hb Constant Spring may or may not be evident by protein methods alone dependent upon the percentage present. It is important to note, alpha-thalassemias that are from only 1 or 2 alpha-globin gene deletions are not recognized by protein studies alone and alpha gene deletion and duplication testing is required.

Useful For: Interpretation for the results of hemoglobin electrophoresis Diagnosis and classification of hemoglobin disorders, including thalassemias and hemoglobin variants

Interpretation: Abnormal hemoglobin variants are identified. An interpretive report will be...
Reference Values:
Only orderable as part of a profile. For more information see HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood.

Definitive results and an interpretative report will be provided.

Clinical References:

Hemoglobin Electrophoresis Summary Interpretation
Clinical Information: The evaluation of hemoglobin disorders can be very complex. This can involve abnormalities in the alpha, beta, delta, or gamma chains. Molecular testing is performed to fully evaluate complex situations. A summary interpretation that incorporates all of the testing performed is beneficial to the ordering physician.

Useful For: Incorporating and summarizing results into an overall evaluation with consultative interpretation on the HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values:
Only orderable as a reflex. For more information see HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood.

An interpretive report will be provided.

Clinical References:

Hemoglobin F Distribution, Blood
Clinical Information: More than 75% of the hemoglobin of the newborn is hemoglobin (Hb) F; it diminishes over a period of several months to adult levels, reducing to less than 2% by age 1 and less than 1% by age 2. Hb F may constitute 90% of the total Hb in patients with beta-thalassemia major or other combinations of beta thalassemia and fetal Hb (hereditary persistence of fetal hemoglobin: HPFH)
variants. Hb F is often mildly to moderately elevated in sickle cell disease, aplastic anemia, acute leukemia, and myeloproliferative disorders such as juvenile myelomonocytic leukemia (JMML), hereditary spherocytosis, and alpha-thalassemia minor. It is commonly increased in hemoglobinopathies associated with hemolysis. Hb F increases to as high as 10% during normal pregnancy. Hb F is also increased due to medications such as hydroxyurea, decitabine, and lenalidomide. Elevation in Hb F has been cited as a discriminator between Diamond-Blackfan congenital pure red cell aplasia (elevated) and transient erythroblastopenia of childhood (normal), but whether this simply reflects the chronicity of anemia inherent to the former condition rather than a specific finding is unclear. In the common (large deletional) form of the genetic trait HPFH, all of the erythrocytes contain Hb F. When tested by flow cytometry using specificity for Hb F, these HPFH cases display a homocellular distribution pattern of Hb F within the red cell population. Other causes of increased Hb F including delta beta thalassemia, hydroxyurea, and some nondeletional HPFH variants typically display a heterocellular distribution of Hb F within the erythrocytes, reflecting disparate populations of F cells and cells lacking Hb F. Quantification of Hb F percentage should be determined prior to flow cytometry of Hb F red cell distribution to establish the appropriateness of this test. The flow cytometry analysis of elevated Hb F levels is useful when Hb F percentage is 15% to 35% and the clinical differential diagnosis includes large deletional HPFH. Hb F percentages below 15% are likely not due to large deletional HPFH, and causes of Hb F percentages above 35% are better confirmed by molecular and family studies.

**Useful For:** Distinguishing large deletional hereditary persistence of fetal hemoglobin from other conditions with increased percentage of fetal hemoglobin (Hb F) Determining the distribution of Hb F within red blood cells

**Interpretation:** Homocellular distribution of fetal hemoglobin (Hb) is found in large deletional hereditary persistence of fetal Hb (HPFH). Heterocellular distribution is found in delta beta thalassemia, medication induced, and other causes of increased Hb F.

**Reference Values:**
Only orderable as a reflex. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood

Reported as heterocellular or homocellular

**Clinical References:**

**Hemoglobin Stability, Blood**

**Clinical Information:** Unstable hemoglobin disease is rare and may be caused by any 1 of a large number of hemoglobin variants. They are inherited as an autosomal dominant trait. The severity of the disease varies according to the hemoglobin variant; there may be no clinical symptoms or the disease may produce a mild, moderate, or severe hemolytic anemia. The stained peripheral blood smear shows anisocytosis, poikilocytosis, basophilic stippling, polychromasia and, sometimes, hypochromia. The reticulocyte count may be increased. Splenomegaly and Heinz bodies may also be present.
Hemoglobin Variant, A2 and F Quantitation, Blood

Clinical Information: The treatment of red blood cell sickling disorders may involve many therapeutic modalities. Two of the most important and beneficial are treatment with hydroxyurea and chronic transfusion therapy. Hydroxyurea causes elevation of fetal hemoglobin (Hb F) levels, and transfusion serves to lower the percentage of hemoglobin S (Hb S). Both of these therapeutic modalities act to lessen the number and severity of sickling crises. Thus, periodic monitoring of Hb F and Hb S levels are needed to guide further therapy.

Useful For: Monitoring patients with sickling disorders who have received hydroxyurea or transfusion therapy This test is not intended for diagnostic purposes. This test is not useful for screening purposes.

Interpretation: Clinically, optimal levels of hemoglobin S (Hb S) and fetal hemoglobin (Hb F) are patient specific and depend on a number of factors including response to therapy. This test will be performed by capillary electrophoresis and any detected variant present will be reported as their zone only, including Hb S. No confirmatory functional study, such as sickle solubility, will be performed as this test is designed for quantitative monitoring of previously confirmed hemoglobin fractions. Information reported: Percentages of hemoglobin A (Hb A), hemoglobin A2 (Hb A2), Hb F and any detected hemoglobin variant present. Variants will be reported as zones and are not specific, even if present in Z5 (Zone S). If the identity of the variant has not been previously confirmed, diagnostic hemoglobin electrophoresis testing is necessary (see HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood).

Reference Values:

<table>
<thead>
<tr>
<th>Hemoglobin A</th>
<th>1-30 days: 5.9-77.2%</th>
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<tbody>
<tr>
<td></td>
<td>1-2 months: 7.9-92.4%</td>
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</tr>
<tr>
<td></td>
<td>&gt; or =24 months: 95.8-98.0%</td>
</tr>
</tbody>
</table>

| Hemoglobin A2 | 1-30 days: 0.0-2.1% |
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%
> or =6 months: 2.0-3.3%

HEMOGLOBIN F
1-30 days: 22.8-92.0%
1-2 months: 7.6-89.8%
3-5 months: 1.6-42.2%
6-8 months: 0.0-16.7%
9-12 months: 0.0-10.5%
13-17 months: 0.0-7.9%
18-23 months: 0.0-6.3%
> or =24 months: 0.0-0.9%

VARIANT 1
0.0

VARIANT 2
0.0

VARIANT 3
0.0

Clinical References:

Hemoglobin, Blood

Clinical Information: Hemoglobin transports oxygen and CO2. This activity is decreased in anemia and increased in polycythemia, erythrocytosis, and dehydration. Hemoglobin measurements are used as clinical guides in the diagnosis or monitoring of many diseases.

Useful For: Screening tool to confirm a hematologic disorder Establishing or ruling out a diagnosis Detecting an unsuspected hematologic disorder Monitoring the effects of radiation or chemotherapy

Interpretation: Results outside of normal value ranges may reflect a primary disorder of the cell-producing organs or an underlying disease. Results should be interpreted in conjunction with the patient's clinical picture and appropriate additional testing performed.

Reference Values:
HEMOGLOBIN
Males:
0-14 days: 13.9-19.1 g/dL
15 days-4 weeks: 10.0-15.3 g/dL
5 weeks-7 weeks: 8.9-12.7 g/dL
8 weeks-5 months: 9.6-12.4 g/dL
6 months-23 months: 10.1-12.5 g/dL

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Hemoglobin, Qualitative, Random, Urine

Clinical Information: Free hemoglobin (Hb) in urine usually is the result of lysis of red blood cells present in the urine due to bleeding into the urinary tract (kidney, ureters, bladder). Less commonly, intravascular hemolysis (e.g., transfusion reaction, hemolytic anemia, paroxysmal hemoglobinuria) may result in excretion of free Hb from blood into urine. Injury to skeletal or cardiac muscle results in the release of myoglobin, which also is detected by this assay. Conditions associated with myoglobinuria include hereditary myoglobinuria, phosphorylase deficiency, sporadic myoglobinuria, exertional myoglobinuria in untrained individuals, crush syndrome, myocardial infarction, myoglobinuria of progressive muscle disease, and heat injury.

Useful For: Screening for hematuria, myoglobinuria, or intravascular hemolysis

Interpretation: Free hemoglobin (Hb), in the presence of red blood cells (RBC), indicates bleeding into the urinary tract. Free Hb, in the absence of RBC, is consistent with intravascular hemolysis. Note: RBC may be missed if lysis occurred prior to analysis; the absence of RBC should be confirmed by examining a fresh specimen. The test is equally sensitive to hemoglobin and to myoglobin. The presence of myoglobin may be confirmed by MYGLU / Myoglobin, Random, Urine.

Reference Values:
COLOR: Colorless, Yellow
CLARITY: Clear
CONCISTENCY: Not reported
HEMOGLOBIN: Negative
Red Blood Cells: <3 RBC/hpf
Hemoglobinopathy Interpretation

Clinical Information: This consultative study is primarily designed for the evaluation of microcytosis but also has the ability to test for the detection of almost all known hemoglobin disorders in an economical manner. Because this can include multiple tests for alpha-thalassemias, beta-thalassemias, delta-beta-thalassemia, hereditary persistence of fetal hemoglobin (HPFH), and for all known hemoglobin (Hb) variants, an expert in these disorders can guide testing to explain the clinical question or reported complete blood count values. This evaluation is particularly useful for complete classification of compound combinations of Hb S with alpha- or beta-thalassemia, Hb E/beta-0-thalassemia, and many other complex alpha and beta thalassemia disorders. Since iron deficiency can mimic thalassemias, ferritin levels are measured to evaluate this possibility, if a serum sample is received. Hb disorders include those associated with thalassemias (decreased protein quantity) and Hb variants (abnormal protein production). Many are clinically harmless and others cause symptoms including microcytosis, sickling disorders, hemolysis, erythrocytosis, cyanosis/hypoxia, long-standing or familial anemia, compensated or episodic anemia, and increased methemoglobin or sulfhemoglobin results. Hb disorders can show patterns of either autosomal recessive or autosomal dominant inheritance. The thalassemias are a group of disorders of Hb synthesis. Normal adult Hb consists of 2 alpha globin chains (encoded by 2 pairs of alpha globin genes, each pair located on chromosome 16), and 2 beta globin chains (encoded by 2 beta globin genes, each located on chromosome 11). Thalassemia syndromes result from an underproduction of 1 or 2 types of globin chains and are characterized by the type (alpha, beta, delta, gamma), magnitude of underproduction (number of defective genes), and the severity of clinical symptoms (minor, intermedia, major). The severity of the clinical and hematologic effects is directly related to the imbalance of alpha-like to beta-like chains. The most common form of thalassemia is alpha thalassemia. Alpha thalassemia usually involves deletion of entire alpha genes, and varies in severity depending on the number of alpha chains deleted (or rendered nonfunctional). Alpha thalassemia trait usually results from the deletion of 2 alpha genes. The most common form of Hb H disease results from dysfunction of 3 alpha chains and shows a variable phenotype, with most cases showing moderate anemia. The deletion of all 4 alpha genes (Barts hydrops fetalis) is incompatible with life without significant medical intervention. Non-deletion alpha thalassemia genetic variants can also result in either thalassemia trait or Hb H disease and are less common than deletion forms. Conversely most beta thalassemia genetic variants are due to single nucleotide substitutions that can occur anywhere in the beta globin gene. Large deletions of the beta globin gene complex can result in elevations in Hb F, such as hereditary persistence of fetal hemoglobin (HPFH) or delta-beta thalassemia. While the presence of a single beta gene variant (beta thalassemia trait) results primarily in RBC microcytosis, cases with two beta gene abnormalities show a wide range in clinical severity, and many cases require molecular testing to understand the phenotype.

Useful For: Interpretation of results for the evaluation of thalassemias and hemoglobinopathies
Evaluation of microcytosis Extensive and economical diagnosis and classification of hemoglobinopathies or thalassemia including complex disorders Diagnosis of hereditary persistence of hemoglobin (HPFH)

Interpretation: A hematopathologist expert in these disorders evaluates the case and an interpretive report is issued.

Reference Values: Only orderable as part of a profile. For more information see THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood.

Definitive results and an interpretive report will be provided.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Hemolytic Anemia Evaluation, Blood

Clinical Information: Hemolytic anemia (HA) is characterized by increased red cell destruction and a decreased red cell life span. Patients usually have decreased hemoglobin concentration, hematocrit, and red blood cell count, but some can have compensated disorders, and symptoms such as reticulocytosis, pigmented gallstones, and decreased haptoglobin are factors that raise clinical suspicion. Blood smear abnormalities may include variable amounts of poikilocytosis including spherocytes, elliptocytes, schistocytes, stomatocytes, echinocytes, polychromasia, basophilic stippling, and target cells. Osmotic fragility can be increased due to the presence of spherocytes. These are all nonspecific features that can be present in both hereditary and acquired hemolytic disorders. Inherited hemolytic disorders may include red cell membrane disorders, red cell enzyme defects, or abnormalities in the hemoglobin molecule in the red cell. This panel assesses for possible causes of congenital/hereditary causes of hemolytic anemia and does not evaluate for acquired causes. Therefore, the anemia should be lifelong or familial in nature. Examples of acquired HA include: autoimmune HA (Coombs-positive HA, Coombs-negative autoimmune HA), cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, mechanical hemolysis (aortic stenosis or prosthetic heart valves), disseminated intravascular coagulation/thrombotic microangiopathy, and drug-induced HA. This consultation evaluates for a hereditary cause of increased red cell destruction and includes testing for red cell membrane disorders, such as hereditary spherocytosis and hereditary pyropoikilocytosis, hemoglobinopathies, and red cell enzyme abnormalities. This panel is of limited use in patients with a history of recent transfusion and should be ordered as remote a date from transfusion as possible in those patients who are chronically transfused.

Useful For: Evaluation of lifelong or inherited hemolytic anemias, including red cell membrane disorders, unstable or abnormal hemoglobin variants, and red cell enzyme disorders. This evaluation is not suitable for acquired causes of hemolysis.

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Definitive results and an interpretive report will be provided.

Clinical References:
Hemolytic Anemia Interpretation

Clinical Information: Hemolytic anemia (HA) is characterized by increased red cell destruction and a decreased red cell life span. Patients usually have decreased hemoglobin concentration, hematocrit, and red blood cell count, but some can have compensated disorders, and symptoms such as reticulocytosis, pigmented gallstones, and decreased haptoglobin are factors that raise clinical suspicion. Blood smear abnormalities may include variable amounts of poikilocytosis including spherocytes, elliptocytes, schistocytes, stomatocytes, echinocytes, polychromasia, basophilic stippling, and target cells. Osmotic fragility can be increased due to the presence of spherocytes. These are all nonspecific features that can be present in both hereditary and acquired hemolytic disorders. Inherited hemolytic disorders may include red cell membrane disorders, red cell enzyme defects, or abnormalities in the hemoglobin molecule in the red cell. This panel assesses for possible causes of congenital/hereditary causes of hemolytic anemia and does not evaluate for acquired causes. Therefore, the anemia should be lifelong or familial in nature. Examples of acquired HA (which should be excluded prior to ordering this panel) include: autoimmune HA (Coombs-positive HA, Coombs-negative autoimmune HA), cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, mechanical hemolysis (aortic stenosis or prosthetic heart valves), disseminated intravascular coagulation/thrombotic microangiopathy, and drug-induced HA. This consultation evaluates for a hereditary cause of increased red cell destruction and includes testing for red cell membrane disorders, such as hereditary spherocytosis and hereditary pyropoikilocytosis, hemoglobinopathies, and red cell enzyme abnormalities. This panel is of limited use in patients with a history of recent transfusion and should be ordered as remote a date from transfusion as possible in those patients who are chronically transfused.

Useful For: Interpretation of the results for the evaluation of hemolytic anemia Evaluation of lifelong or inherited hemolytic anemias, including red cell membrane disorders, unstable or abnormal hemoglobin variants, and red cell enzyme disorders

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Only orderable as part of a profile. For more information see HAEV1 / Hemolytic Anemia Evaluation, Blood.

Definitive results and an interpretive report will be provided.

Hemolytic Anemia Summary Interpretation

Clinical Information: The evaluation of patients with hemolytic anemia can be very complex and involves incorporation of not only testing, but integration of clinical and peripheral blood findings. Nonimmune hemolytic anemia can be due to many causes, including abnormalities in the hemoglobin molecule, RBC membrane/cytoskeleton, or RBC enzyme cascade. If the evaluation of nonimmune hemolytic anemia utilizes the reflex molecular tests, a summary interpretation will be added to summarize the genetic, protein, peripheral blood, and clinical findings (if provided) will be added. This is beneficial to the ordering provider.

Useful For: Incorporating and summarizing subsequent results into an overall evaluation if 1 or more molecular tests are reflexed on the HAEV1 / Hemolytic Anemia Evaluation, Blood panel

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values: Only orderable as a reflex. For more information see HAEV1 / Hemolytic Anemia Evaluation, Blood.

An interpretation report will be provided.

**Analysis, Prenatal**

**Clinical Information:** Hemophilia A (HA) is due to a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 and 22 inversion mutations account for approximately 50% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** Prenatal testing for hemophilia A when a mutation has not been identified in the family.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** Not applicable

males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** First-tier molecular testing for males affected with severe hemophilia A when a mutation has not been identified in the family Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A

**Interpretation:** The interpretive report will include assay information, background information, and conclusions based on the test results.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**F81P**

**Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation Analysis, Prenatal, Varies**

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding is the most common clinical symptom in individuals with HA and correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion mutation accounts for approximately 5% of mutations associated with severe HA. This inversion is typically not identified in patients with mild or moderate HA. Intron 1 inversion known mutation analysis on a prenatal specimen can only be performed when there is a known intron 1 inversion in the family. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** Prenatal testing for hemophilia A when a F8 intron 1 inversion has been identified in a family member.

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Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation, Whole Blood

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion mutation accounts for approximately 5% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 1 inversion known mutation analysis is only recommended for individuals when an intron 1 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 1 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: First-tier molecular testing for males affected with severe hemophilia A, when a familial intron 1 inversion has been previously identified Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A due to F8 intron 1 inversion

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values: An interpretive report will be provided.

Hemophilia A F8 Gene, Intron 22 Inversion Known Mutation, Whole Blood

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion mutations account for approximately 45% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known mutation analysis is only recommended for individuals when an intron 22 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 22 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** First-tier molecular testing for males affected with severe hemophilia A, when a familial intron 22 inversion has been previously identified Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A due to F8 intron 22 inversion

**Interpretation:** The interpretive report will include assay information, background information, and conclusions based on the test results.

**Reference Values:**
An interpretive report will be provided.

Hemophilia A F8 Gene, Intron 22 Inversion Mutation Analysis, Prenatal, Varies

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion mutations account for approximately 45% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known mutation analysis on a prenatal specimen can only be performed when there is a known intron 22 inversion in the family. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: Prenatal testing for hemophilia A when a F8 intron 22 inversion has been identified in a family member.

Interpretation: An interpretive report will be provided.

Reference Values: Not applicable

Clinical References:

Hemophilia A, F8 Gene, Next-Generation Sequencing, Varies

Clinical Information: Hemophilia A (HA) is a bleeding diathesis that most commonly affects male individuals. Symptoms include soft tissue bleeding and articular hemorrhage, such as joint bleeds, deep muscle hematomas, intracranial bleeding, prolonged oozing after surgery, and unexplained gastrointestinal (GI) bleeding. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. In severe hemophilia, affected male patients typically present with these symptoms within the first 2 years of life. In moderate hemophilia, affected male patients will usually present in their toddler years. Mild hemophiliacs are typically diagnosed later in life and sometimes well into adulthood. HA is an X-linked recessive disorder that affects approximately 1 in 10,000 live male births, among all ethnic populations. Female carriers of HA alterations have a 50% chance of passing on the alteration to each child they have. If the child is male, there is a 50% chance of him inheriting the alteration and being affected by HA. If the child is female, there is a 50% chance of her inheriting the alteration and being a carrier of HA. While female carriers generally do not have bleeding symptoms, they are at risk of having affected sons.
However, not all women with an affected son are germline carriers of a F8 alteration as de novo alterations in F8 occur. Overall, there is a 2% to 20% chance of her not being a carrier of an alteration associated with HA, depending on the type of alteration in the son. Importantly, there is a small risk for recurrence even when the familial F8 alteration is not identified in the mother of the affected patient due to the possibility of germline mosaicism. All of the daughters of a man with HA will inherit the disease-causing alteration. None of his sons will inherit the alteration or be affected by HA. Daughters of a man with hemophilia are considered obligate carriers because it is a virtual certainty that they carry the alteration by virtue of their biological relationship with their father. If a woman has a brother or maternal nephew who is affected with hemophilia and then has a son with hemophilia, she too is considered an obligate carrier. HA is caused by a deficiency of clotting factor VIII (FVIII), an essential blood coagulation protein. Factor VIII increases the catalytic activity of factor IXa to convert factor X to Xa by more than 100,000-fold, propelling further steps in the coagulation cascade. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have an alteration in F8. Hemophilia is classified according to bleeding severity, which correlates with FVIII activity levels. Severe HA is associated with FVIII activity levels of less than 1% in a male. Moderate HA is associated with 1% to 5% activity. Mild hemophilia is associated with 5% to 40% of factor VIII activity. Affected male patients are diagnosed with hemophilia A on the basis of their FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier female patients are identified by family history assessment. For affected male patients, genetic testing to identify the causative alteration is indicated if factor studies confirm an abnormally low FVIII clotting activity (less than 40%) and von Willebrand factor antigen testing is normal. In affected male patients, there is good correlation between genotype, FVIII plasma levels, and hemorrhagic risk. Genetic testing for HA in women should only be considered if she has a first-degree male relative diagnosed with HA, or if she has abnormally low FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma). Carrier status in females is not excluded if the female patient has normal FVIII activity. In females, the wide range of normal factor FVIII activity in women precludes an accurate assessment of carrier status, thus making molecular testing essential in assessment of carrier status in women maternally related to males affected by HA. Carrier testing is made much easier and conclusive when the specific familial alteration has been identified in an affected male relative of obligate carrier. For prenatal testing, a specific familial alteration should be known in order to perform prenatal testing on any male fetus at risk of inheriting a genetic alteration causing hemophilia from his mother. This is because diagnostic prenatal testing requires an invasive procedure (ie, amniocentesis or chorionic villi sampling) that carries a small but real risk of inducing spontaneous abortion. Thus, prior to any prenatal genetic testing, every effort should be made to 1) identify the familial alteration in an affected male relative or in an obligate carrier and 2) confirm the mother carries the alteration. This ensures an invasive procedure is not performed unnecessarily on a pregnancy that is not at risk for hemophilia and that the test results are informative and conclusive. Causes of acquired (non-genetic) HA that should be excluded prior to genetic testing include heparin use, disorders associated with antibodies to clotting factors such as systemic lupus erythematosus or antiphospholipid syndrome, pregnancy or the postpartum period, rheumatic disease, tumors or hematologic malignancies, use of certain drugs (eg, penicillin, sulfamides, phenytoin, interferon, fludarabine). Obtaining a medical genetics or hematology (coagulation) consultation prior to ordering is advised.

**Useful For:** Molecular confirmation of a clinical diagnosis of hemophilia A in affected male patients Identification of the causative alteration in the F8 gene for prognostic and genetic counseling purposes Helping determine hemophilia A carrier status for female patients with a family history of hemophilia A Molecular prenatal confirmation of hemophilia A

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**
An interpretive report will be provided

Hemophilia B, F9 Gene Known Mutation Analysis, Prenatal

Clinical Information: Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves, and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of hemophilia B patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX:antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

Useful For: Prenatal testing for a known familial pathogenic mutation in the F9 gene in a fetus who is at risk for inheriting this mutation

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be issued that will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation).


Hemophilia B, F9 Gene Known Mutation, Whole Blood

Clinical Information: Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female
offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves, and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX antigen.

More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

**Useful For:** Diagnostic, targeted testing for hemophilia B when a mutation has been identified in a family member Carrier testing of females in whom the familial F9 genotype is known

**Interpretation:** The interpretive report will include assay information, background information, and conclusions based on the test results.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**NGSF9**

**606365**

**Hemophilia B, F9 Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Hemophilia B is a bleeding diathesis that most commonly affects males. Symptoms include soft tissue bleeding and articular hemorrhage, such as joint bleeds, deep muscle hematomas, intracranial bleeding, prolonged oozing after surgery, and unexplained gastrointestinal (GI) bleeding. In males with severe deficiency, spontaneous bleeding may occur. Males affected by severe hemophilia B typically present with these symptoms within the first 2 years of life. In individuals with mild hemophilia B, bleeding may occur only after surgery or trauma. Hemophilia B is an X-linked recessive disorder that affects 1 in 30,000 live male births across all ethnic groups. Female carriers of hemophilia B have a 50% chance of passing on the alteration to each child they have. If the child is male, there is a 50% chance of him inheriting the alteration and being affected by hemophilia B. If the child is female, there is a 50% chance of her inheriting the alteration and being a carrier of hemophilia B. While most female carriers of hemophilia B do not have bleeding symptoms, they are at risk of having affected sons. However, not all females with an affected son and no other family history of the disease are germline carriers of a F9 alteration as de novo alterations in F9 occur. Importantly, there is a small risk for recurrence even when the familial F9 alteration is not identified in the mother of the affected patient due to the possibility of germline mosaicism. All of the daughters of a man with hemophilia B will inherit the disease-causing alteration. None of his sons will inherit the alteration or be affected by hemophilia B. Daughters of a man with hemophilia are considered obligate carriers because it is a virtual certainty that they carry the alteration by virtue of their biological relationship with their father. If a woman has a brother or maternal nephew who is affected with hemophilia and then has a son with hemophilia, she too is considered an obligate carrier. Hemophilia B is caused by a deficiency of clotting factor IX (FIX), an essential blood coagulation protein that is synthesized in the liver and circulates in plasma as an inactive zymogen. The main function of factor IX is to activate factor X to Xa, initiating thrombin formation necessary for the creation of an insoluble hemostatic thrombus at the site of vascular injury to help stop bleeding. FIX is encoded by the factor IX (F9) gene. Alterations in the F9 gene that reduce the amount of circulating FIX or result in the impairment of its function lead to the inability to form a clot to stop bleeding at the site of injury. Additionally, there are several unusual FIX variants that cause atypical
phenotypes, such as hemophilia B Leyden (associated with age-dependent bleeding severity), the c.109G>A; p.Ala37Thr alteration (which induces warfarin sensitivity), and FIX Padua (p.Arg384Leu; associated with thrombophilia). Hemophilia B is classified according to bleeding severity, which correlates with FIX activity levels. Severe hemophilia B is associated with FIX activity levels of less than 1%. Moderate hemophilia B is associated with 1% to 5% activity. Mild hemophilia is associated with 5% to 40% of factor IX activity. Affected males are diagnosed with hemophilia B on the bases of their FIX activity (F_9 / Coagulation Factor IX Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. For affected males, genetic testing to identify the causative mutation is indicated if factor studies confirm an abnormally low FIX clotting activity (less than 40%). In affected males, there is good correlation between genotype, FIX plasma levels, and hemorrhagic risk. Genetic testing for hemophilia B in females should only be considered if she has a first-degree male relative diagnosed with hemophilia B, if there is a maternal family history of hemophilia B and her mother has not been excluded as a carrier, or if she has abnormally low FIX (F_9 / Coagulation Factor IX Activity Assay, Plasma). Carrier status in females is not excluded if the female patient has normal FIX activity. In females, the wide range of normal factor FIX activity in women precludes an accurate assessment of carrier status, thus making molecular testing essential in assessment of carrier status in women maternally related to males affected by hemophilia B. Carrier testing is made much easier and conclusive when the specific familial alteration has been identified in an affected male relative of obligate carrier. For prenatal testing, a specific familial alteration should be known in order to perform prenatal testing on any male fetus at risk of inheriting a genetic alteration from his mother. This is because diagnostic prenatal testing requires an invasive procedure (ie, amniocentesis or chorionic villi sampling) that carries a small but real risk of inducing spontaneous abortion. Thus, prior to any prenatal genetic testing, every effort should be made to 1) identify the familial alteration in an affected male relative or in an obligate carrier and 2) confirm the mother carries the alteration. This ensures an invasive procedure is not performed unnecessarily on a pregnancy that is not at risk for hemophilia and that the test results are informative and conclusive. Causes of acquired (non-genetic) factor IX deficiency that should be excluded prior to genetic testing include vitamin K deficiency. Given that FIX is a vitamin K-dependent protein, all patients with mild to moderate reductions in FIX activity should have vitamin K deficiency excluded. In addition, healthy normal children have a lower FIX activity that reaches adult reference ranges at puberty. A handful of cases have been described that involve an acquired deficiency of factor IX (acquired hemophilia B) related to an autoimmune disorder. Obtaining a medical genetics of hematology (coagulation) consultation prior to ordering is advisable.

**Useful For:** Molecular confirmation of a clinical diagnosis of hemophilia B in affected male patients
Identification of the causative alteration in the F9 gene for prognostic and genetic counseling purposes
Helping determine hemophilia B carrier status for female patients with a family history of hemophilia B
Molecular prenatal confirmation of hemophilia B

**Interpretation:** An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Hemophilia C, F11 Gene, Next-Generation Sequencing, Varies

Clinical Information: Factor XI deficiency (FXID) is a bleeding diathesis that is also known as hemophilia C. FXID produces a bleeding disorder that is relatively mild, rarely spontaneous, and associated with certain sites of the body, namely the oral cavity, nasopharynx, and urinary tract. Bleeding frequency and severity are highest when trauma or certain surgical procedures involve tissues in these areas. Menorrhagia and nose bleeds are common. Overall, in the general population, the prevalence of severe FXID is 1 per million. However, FXID is common in certain ethnic groups. In Ashkenazi Jews, severe deficiency is found in 1 in 450 people. Founder mutations are also found among French Basques and French individuals from Nantes. Hereditary FXID is typically inherited in an autosomal recessive manner. However, some rare alterations exert a dominant-negative effect or interfere with the functioning of normal factor XI (FXI), causing an autosomal dominant bleeding disorder. FXID is a result of defects in the concentration or function of coagulation FXI, which is synthesized in the liver and circulates in blood plasma as an inactive zymogen. The role of activated FXI includes sustained activation of factor IX, leading to fibrin formation and clot stability, especially in tissues with high fibrinolytic activity, such as oral cavity, nasopharynx, and urinary tract. A significant deficiency in the amount of functional FXI can cause excessive bleeding in these tissues after trauma or certain surgical procedures. FXID is defined as severe when FXI activity is less than 15% (15 U/dL). It is considered moderate when it is between 15% and 50% (15 to 50 U/dL). However, plasma FXI activity levels to do not correlate well with bleeding phenotype, in part activity levels appear unable to reflect true physiological activity of FXI (eg, p.Ser266Asn is associated with bleeding and defective FXI binding to platelets but is reported not affect aPTT). Some patients with 15% to 50% FXI activity present similarly to severely deficient patients, indicating contributing factors to disease severity, eg, the qualities of the specific alteration(s) underlying the disorder or the co-inheritance of other bleeding disorders. Of note, normal, full-term newborn infants or healthy premature infants may have decreased levels (greater than or equal to 10%) that may not reach adult levels for greater than or equal to 180 days after birth. The F11 gene encodes FXI. Genetic testing for pathogenic alterations in F11 is indicated if FXI activity is below 50% of normal. Patients lacking FXI will also typically have very long activated partial thromboplastin times (aPTT). Acquired FXID appears to be a rare complication of liver disease. Liver disease should be excluded prior to genetic testing.

Useful For: Genetic confirmation of a factor XI deficiency diagnosis with the identification of known or suspected pathogenic alterations in the F11 gene Carrier testing for close family members of an individual with a factor XI deficiency diagnosis This test is not intended for prenatal diagnosis

Interpretation: An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Reference Values: An interpretive report will be provided

**Clinical Information:** Several noninvasive tests are available to detect gastrointestinal (GI) bleeding. However, guaiac type and immunochemical tests for occult bleeding are affected by the presence of reducing or oxidizing substances and are insensitive for the detection of upper GI tract (esophagogastric) bleeding, where most clinically significant occult GI bleeding occurs. The HemoQuant test is the most reliable, noninvasive test currently available for detecting bleeding of the esophago-GI tract. Unlike other tests for blood in feces, this test detects both intact heme and porphyrins from partly degraded heme. Additionally, test results are not complicated by either the water content of the specimen or the presence of reducing or oxidizing substances. Furthermore, HemoQuant testing is sensitive to both proximal and distal sources of occult GI bleeding. HemoQuant is the most appropriate fecal occult blood test to use in the evaluation of iron deficiency. Normally, one gram of feces may contain 0.0 - 2.0 mg hemoglobin (Hb); this corresponds to a daily loss of up to 2-mL blood. A demonstration of increased Hb in feces indicates bleeding in the alimentary tract (or ingestion of anticoagulants, aspirin, or red meat).

**Useful For:** Detection of blood in feces Evaluation of iron deficiency Detection of bleeding as a complication of anticoagulant therapy and other medication regimens This test is not specific for bowel cancer.

**Interpretation:** Elevated levels are an indicator of the presence of blood in the feces, either from benign or malignant causes.

**Reference Values:**

- Normal: 
  - < or =2.0 mg total hemoglobin/g feces
- Marginal:
  - 2.1-4.0 mg total hemoglobin/g feces*
- *2.1-4.0 mg Hb/g is considered marginally elevated, but not clinically significant, if red meat, warfarin, or aspirin was ingested 72 hrs prior to collection.
- Elevated:
  - >4.0 mg total hemoglobin/g feces

**Clinical References:**


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**Hemosiderin, Random, Urine**

**Clinical Information:** When the plasma hemoglobin level is 50 to 200 mg/dL after hemolysis, the capacity of haptoglobin to bind hemoglobin is exceeded, and hemoglobin readily passes through the glomeruli of the kidney. Part of the hemoglobin is absorbed by the proximal tubular cells where the hemoglobin iron is converted to hemosiderin. When these tubular cells are later shed into the urine, hemosiderinuria results. If the hemoglobin cannot be absorbed into the tubular cells, hemoglobinuria results. Hemosiderin is found as yellow-brown granules that are free or in epithelial cells and occasionally in casts in an acidic or neutral urine.

**Useful For:** Detecting hemosiderinuria, secondary to excess hemolysis, as in incompatible blood transfusions, severe acute hemolytic anemia, or hemochromatosis

**Interpretation:** A positive hemosiderin indicates excess red cell destruction. Hemosiderinuria may still be detected after hemoglobin has cleared from the urine and hemoglobin dipstick is negative.

**Reference Values:**
HEMOSIDERIN
Negative

HEMOGLOBIN (internal specimens only)
Negative

RED BLOOD CELLS (internal specimens only)
<3 RBC/hpf


Hemp Western Water (Acnida tamariscina) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 Positive 4 17.50 - 49.99 Strong Positive 5 50.00 - 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

Heparin Anti-Xa, Plasma

Clinical Information: Heparins are sulphated glycosaminoglycans that inactivate thrombin, factor Xa, and several other coagulation factors; act by enhancing activity of the plasma coagulation inhibitor, antithrombin III (AT III); and prolong the activated partial thromboplastin time (APTT). The anti-Xa assay is the preferred method for monitoring low-molecular-weight heparin (LMWH) therapy because of reduced sensitivity of APTT. Heparin is absent in normal plasma. The heparin level obtained has to be analyzed taking into account the treatment given to the patient (type of heparin, dosage, administration mode, time of sampling, etc) and the desired therapeutic effect. It is clinically recommended that platelet counts be monitored frequently in patients receiving unfractionated heparin (UFH) or LMWH in order to detect heparin-induced thrombocytopenia (HIT).

Useful For: Measuring heparin concentration: -In patients treated with low-molecular-weight heparin preparations -In the presence of prolonged baseline activated partial thromboplastin time (APTT) (eg, lupus anticoagulant, "contact factor" deficiency, etc) -When unfractionated heparin dose needed to achieve desired APTT prolongation is unexpectedly higher (>50%) than expected This test is not useful for monitoring therapy with the heparinoid "danaparoid."

Interpretation: Results above the therapeutic range may be supratherapeutic suggesting that the heparin dose may need to be decreased. Results below the therapeutic range may be subtherapeutic suggesting that the heparin dose may need to be increased.

Reference Values:
Adult Therapeutic Range
  UFH therapeutic range: 0.30-0.70 IU/mL
  (6 hours following initiation or dose adjustment)
  LMWH therapeutic range: 0.50-1.00 IU/mL for twice daily dosing*
  LMWH therapeutic range: 1.00-2.00 IU/mL for once daily dosing*
  LMWH prophylactic range: 0.10-0.30 IU/mL
  (*sample obtained 4-6 hours following subcutaneous injection)


**Heparin Cofactor II**

**Clinical Information:** Heparin cofactor II is a glycoprotein that belongs to the serine protease inhibitor family. Heparin cofactor II, also known as heparin cofactor A or dermatan sulfate cofactor, has a molecular weight of approximately 65 kilodaltons and has a plasma concentration of 9 mg/dL. Heparin cofactor II is synthesized by the liver and has a plasma half-life of 60 hours. Heparin cofactor II specifically inhibits thrombin, in contrast to antithrombin, which inhibits thrombin, factor Xa, and other serine proteases. The inhibition of thrombin by heparin cofactor II is approximately 10 times slower than antithrombin-mediated inhibition and occurs through the formation of equimolar complexes between the reactive site of the inhibitor and the active site of thrombin. The antithrombotic activity of heparin cofactor II is greatly enhanced (over 1000-fold) in the presence of heparin and dermatan sulfate. The physiologic function of the molecule is unclear, but its role may be to serve as an antithrombotic agent in the presence of dermatan sulfate. Acquired deficiencies of heparin cofactor II are reported in patients with liver disease and disseminated intravascular coagulation. Conversely, increased levels of heparin cofactor II may be observed in individuals with renal disorders with proteinuria, during pregnancy, and with oral contraceptive usage. Inherited deficiency of heparin cofactor II has been reported in rare instances and is inherited as an autosomal dominant trait. A clear relationship between increased risk of thrombosis and heparin cofactor II deficiency has not been established since deficiency of heparin cofactor II is observed in both healthy individuals and those with thrombotic episodes. Limited studies have shown that heterozygosity for heparin cofactor II is not a likely risk for thrombosis without other concomitant risk factors. Other studies have reported thrombotic episodes in 36% of individuals with the deficiency.

**Useful For:** Assessment of thrombotic risk associated with heparin cofactor II levels.

**Reference Values:**

- 65-145%

In healthy adults, heparin cofactor II reference range in plasma is 65% to 145%. Plasma levels of heparin cofactor II are approximately 50% of adult levels at birth and reach adult levels at six months of age.

**Heparin-PF4 IgG Antibody, Serum**

**Clinical Information:** There are established and emerging disorders that are collectively termed thrombocytopenia and thrombosis syndromes, which most commonly include: heparin induced thrombocytopenia, which occurs after exposure to heparin, unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Additional newer associations include vaccine induced thrombocytopenia, which rarely occurs after exposure to adenovirus vector severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, and spontaneous or autoimmune heparin platelet-factor 4 (PF4) IgG antibody, which occurs without exposure to UFH/LMWH and typically occurs after surgery or infection. Heparin-induced thrombocytopenia (HIT) consists of 2 distinct clinicopathologic syndromes. The first, sometimes designated type I HIT (HIT-I) or nonimmune heparin-associated thrombocytopenia (HAT), is a common benign condition that is not immunologically mediated. Type I HIT is characterized by a mild decrease of the platelet count (typically < or =30%
autoimmune HIT: Patients typically present a week to 10 days after surgery or viral infections with thrombocytopenia could occur within 24 to 48 hours after reexposure to heparin. Spontaneous or (especially within the preceding 100 days): in addition to the above findings, the onset of beginning approximately 5 to 10 days after initiation of heparin this may or may not be associated with (thrombocytopenia) of 50% or more from baseline or postoperative peak. 2) Onset of thrombocytopenia picture of immune HIT HIT: In patients not previously exposed to heparin: 1) decrease in platelet count adenovirus vector SARS-CoV-2 exposure. The clinical course is also similar to immune HIT. Clinical other syndromes of thrombocytopenia and thrombosis: There are an increasing number of reports of ELISA result has relatively low and uncertain predictive value for the development of clinical HIT-II. Of all patients prior to, during, or following heparin use is currently not recommended. A positive H/PF4 antibodies and are based on the detection of human antibodies that react with solid phase antigen complexes of heparinoid and human PF4 (H/PF4 complexes). The ELISA for H/PF4 antibodies is very sensitive for antibody detection but relatively nonspecific for clinical HIT diagnosis. Routine screening of all patients prior to, during, or following heparin use is currently not recommended. A positive ELISA result has relatively low and uncertain predictive value for the development of clinical HIT-II. Other syndromes of thrombocytopenia and thrombosis: There are an increasing number of reports of patients who develop thrombocytopenia and thrombosis after surgery, particularly after orthopedic surgery and after selected infections. The clinical course of this group of patients is similar to the classical HIT occurring with heparin exposure. An emerging recognition is the development of thrombocytopenia and thrombosis occurring predominantly in young females within 3 to 4 weeks after adenovirus vector SARS-CoV-2 exposure. The clinical course is also similar to immune HIT. Clinical picture of immune HIT HIT: In patients not previously exposed to heparin: 1) decrease in platelet count (thrombocytopenia) of 50% or more from baseline or postoperative peak. 2) Onset of thrombocytopenia beginning approximately 5 to 10 days after initiation of heparin this may or may not be associated with new or progressive thrombosis in patients treated with heparin. Patients previously exposed to heparin (especially within the preceding 100 days): in addition to the above findings, the onset of thrombocytopenia could occur within 24 to 48 hours after reexposure to heparin. Spontaneous or autoimmune HIT: Patients typically present a week to 10 days after surgery or viral infections with
symptoms of thrombosis (venous thromboembolism) or abdominal pain (suggesting adrenal infarction) and thrombocytopenia. Vaccine induced thrombocytopenia and thrombosis: Patients typically present 4 days to 4 weeks after receiving the vaccine. Symptoms may include new onset of severe headache (suggesting cerebral venous sinus thrombosis), abdominal pain (suggesting mesenteric/portal vein thrombosis), or venous/arterial thromboembolism.

Useful For: Detection of IgG antibodies directed against heparin/platelet factor 4 complexes that are implicated in the pathogenesis of immune-mediated type II heparin-induced thrombocytopenia, spontaneous heparin-PF4 IgG antibody (HIT) and thrombocytopenia and thrombosis occurring after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) adenovirus vector vaccine

Interpretation: Results are reported as: 1) Heparin-induced thrombocytopenia (HIT) enzyme-linked immunosorbent assay (ELISA) OD; 2) Heparin inhibition (%); 3) Interpretation. Typical patterns of results and interpretations are depicted in the following table. Interpretive comments will also accompany test reports, when indicated. HIT ELISA OD Heparin inhibition Interpretation Normal range

<table>
<thead>
<tr>
<th>HIT ELISA</th>
<th>Heparin inhibition</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.400</td>
<td>Not done</td>
<td>Negative</td>
</tr>
<tr>
<td>&gt;0.400</td>
<td>or =0.400 or =50%</td>
<td>Positive</td>
</tr>
<tr>
<td>&lt;0.400</td>
<td>or &gt;0.400 &lt;50%</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>

Equivocal A negative result of testing for human platelet factor 4 (H/PF4) antibodies has about a 90% negative predictive value for exclusion of clinical type II heparin-induced thrombocytopenia (HIT-II). Because up to 10% of patients with clinical heparin-induced thrombocytopenia (HIT) may have a negative H/PF4 antibody ELISA result, a negative H/PF4 antibody ELISA result does not exclude the diagnosis of HIT when clinical suspicion remains high. A functional assay for HIT antibodies (eg, heparin-dependent platelet aggregation or serotonin release assay may be helpful in these circumstances). Call 800-533-1710 for ordering information. A positive result is indicative of the presence of H/PF4 complex antibodies. However, this test's specificity is as low as 20% to 50% for clinical diagnosis of HIT, depending on the patient population studied. For example, up to 50% of surgical patients and up to 20% of medical patients treated with heparin may develop H/PF4 antibodies as measured by ELISA, and only a small proportion (1%-5%) develop clinical HIT. Accordingly, this test does not confirm the diagnosis of HIT-II. The diagnosis must be made in conjunction with clinical findings, including evaluation for other potential causes of thrombocytopenia. The presence of H/PF4 antibodies likely increases the risk of clinical HIT, with risk probably partly dependent on associated medical and surgical conditions, but currently there are few data about relative risk of HIT in various populations with positive tests for H/PF4 antibodies.

Reference Values:

HIT ELISA:

<0.400

HIT Interpretation:

Negative

Clinical References:

1. Warkentin TE, Greinacher A, eds: Heparin Induced Thrombocytopenia. Marcel Dekker; 2000:400
once the virus is cleared and may persist for many years.

**Useful For:** Detection of previous exposure or immunity to hepatitis A infection

**Interpretation:** This assay detects the presence of hepatitis A virus (HAV)-specific IgG antibody in serum. A negative result indicates the absence of HAV-specific IgG antibody, implying no past exposure or immunity to HAV infection. A positive result indicates the presence of HAV-specific IgG antibody from either vaccination or past exposure to hepatitis A virus.

**Reference Values:**
- Unvaccinated: negative
- Vaccinated: positive

*See Viral Hepatitis Serologic Profiles in Special Instructions.*

**Clinical References:**
Hepatitis A Qualitative PCR HAV SuperQual

**Clinical Information:** The direct detection of HAV is a valuable tool in determining whether a patient undergoing therapeutic treatment has cleared the virus. It is also useful in determining whether blood or blood products are free of detectable HAV prior to distribution to patients. PCR is able to directly detect HAV RNA and does not rely on later markers such as antigens and antibodies that are not produced in newly infected individuals.

**Useful For:** Detect Hepatitis A Virus RNA (HAV RNA).

**Interpretation:** The presence of target-specific nucleic acid is indicative of infection. Mean Detection: 24.98 copies/mL (12.81 IU/mL) 95% Detection Cutoff: 61.83 copies/mL (31.71 IU/mL)

**Reference Values:** Negative

Hepatitis A Total Antibodies, Serum

**Clinical Information:** Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted primarily by the fecal-oral route, and it is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral routes (eg, exposure to blood) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. In most cases, antibodies to HAV (anti-HAV) are detectable by the time that symptoms occur, usually 15 to 45 days after exposure. Initial antibodies consist almost entirely of the IgM subclass. Anti-HAV IgM usually falls to an undetectable level by 6 months after HAV infection. Anti-HAV IgG levels rise quickly once the virus is cleared and may persist for many years. Currently, commercial diagnostic assays are available for detecting only anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) or anti-HAV total (IgM and IgG), but not anti-HAV IgG alone.

**Useful For:** Detection of recent or previous exposure or immunity to hepatitis A

**Interpretation:** This assay detects the presence of anti-hepatitis A virus (anti-HAV) total (both IgG and IgM combined). A positive result indicates that the patient had hepatitis A either recently or in the past or immunity to hepatitis A from vaccination. If clinically indicated, specific testing for anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) is necessary to confirm the presence of acute or recent hepatitis A. A positive result for anti-HAV total indicates immunity to hepatitis A from either past HAV infection or vaccination against HAV. A negative result indicates the absence of recent or past hepatitis A or a lack of immunity to HAV infection. Borderline test results for anti-HAV total may be seen in: 1) acute hepatitis A with rising levels of anti-HAV IgM, 2) recent hepatitis with rising levels of anti-HAV IgG, or 3) cross-reactivity with nonspecific antibodies (ie, false-positive results). Retesting of both anti-HAV total (HAV / Hepatitis A Total Antibodies, Serum) and anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) is recommended to determine the definitive HAV infection status.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

HEPBC

Hepatitis B Core (HBc) Immunostain, Technical Component Only

Clinical Information: The hepatitis B nucleocapsid contains 2 serologically distinct antigens, the core and the envelope antigen, surrounded by an outer envelope-hepatitis B virus surface antigen. Core antigen is most often present in chronic active hepatitis, compared to surface antigen in the carrier state.

Useful For: Aiding in the identification of hepatitis B infection (chronic active state)

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values: N/A


HBIM

Hepatitis B Core Antibody, IgM, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. In the initial (acute) phase of infection, anti-hepatitis B core antibodies (anti-HBc) consist almost entirely of the IgM antibody class and appear shortly after the onset of symptoms. Anti-HBc IgM antibody can be detected in serum and is usually present for up to 6 months after acute HBV infection. Anti-HBc IgM may be the only serologic marker of a recent hepatitis B infection detectable following the disappearance of hepatitis B surface antigen (HBsAg) and prior to the appearance of hepatitis B surface antibody (anti-HBs) (ie, serologic window period). See Viral Hepatitis Serologic Profiles in Special Instructions.

Useful For: Diagnosis of acute hepatitis B infection Æ Identifying acute hepatitis B virus (HBV) infection in the serologic window period when hepatitis B surface antigen (HBsAg) and antihepatitis B surface (anti-HBs) are negative Æ Differentiation between acute and chronic or past hepatitis B viral infections in the presence of positive anti-hepatitis B core

Interpretation: A positive result indicates recent acute hepatitis B infection. A negative result suggests lack of recent exposure to the virus in preceding 6 months.

Reference Values: Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.

Hepatitis B Core Total Antibodies, Serum

**Clinical Information:** Hepatitis B core antibodies (anti-HBc Ab) appear shortly after the onset of symptoms of hepatitis B infection and soon after the appearance of hepatitis B surface antigen (HBsAg). Initially, anti-HBc Ab consist almost entirely of the IgM class, followed by appearance of anti-HBc IgG, for which there is no commercial diagnostic assay. The anti-HBc total antibodies test, which detects both IgM and IgG antibodies, and the test for anti-HBc IgM antibodies may be the only markers of a recent hepatitis B infection detectable in the "window period." The window period begins with the clearance of HBsAg and ends with the appearance of antibodies to hepatitis B surface antigen (anti-HBs Ab). Anti-HBc total Ab may be the only serologic marker remaining years after exposure to hepatitis B. This assay is FDA-approved for in vitro diagnostic use and not for screening cell, tissue, and blood donors.

**Useful For:** Diagnosis of recent or past hepatitis B infection. Determination of occult hepatitis B infection in otherwise healthy hepatitis B virus (HBV) carriers with negative test results for hepatitis B surface antigen, anti-hepatitis B surface, anti-hepatitis B core IgM, hepatitis Be antigen, and anti-HBe. This assay is not useful for differentiating among acute, chronic, and past or resolved hepatitis B infection. This test is not offered as a screening or confirmatory test for blood donor specimens.

**Interpretation:** A positive result indicates acute, chronic, or past or resolved hepatitis B. An inconclusive result suggests the presence of interfering substance in the patient's serum specimen. Positive anti-hepatitis B core (anti-HBc) total test results should be correlated with the presence of other hepatitis B virus serologic markers, elevated liver enzymes, clinical signs and symptoms, and a history of risk factors. If clinically indicated, testing for HBIM / Hepatitis B Core Antibody, IgM, Serum is necessary to confirm an acute or recent infection. Neonates (<1 month old) with positive anti-HBc total results from this assay should be tested for anti-HBc IgM (HBIM / Hepatitis B Core Antibody, IgM, Serum) to rule out possible maternal anti-HBc causing false-positive results. Repeat testing using this assay for anti-HBc total within 1 month is also recommended in these neonates.

**Reference Values:**

- Negative
  - Interpretation depends on clinical setting.
  - See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

**Hepatitis B Core Total Antibodies, with Reflex to Hepatitis B Core Antibody IgM, Serum**

**Clinical Information:** During the course of a typical case of acute hepatitis B viral (HBV) infection, IgM antibodies to hepatitis B core antigen (anti-HBc IgM) are present in the serum shortly before clinical symptoms appear. Anti-HBc total is detectable during the prodromal, acute, and early convalescent phases when it exists as immunoglobulin M (IgM) anti-HBc. Anti-HBc IgM rises in level and is present during the core window period, i.e., after hepatitis B surface antigen disappears and before antibodies to hepatitis B surface antigen appear. Anti-HBc total may be the only serologic marker remaining years after exposure to HBV.

**Useful For:** Detection and differentiation between recent and past/resolved or chronic hepatitis B viral (HBV) infection Diagnosis of recent HBV infection during the "window period" when both hepatitis B surface antigen (HBsAg) and antibodies to HBsAg are negative This test is not useful for determining immunity to or recovery from hepatitis B viral (HBV) infection.

**Interpretation:** Positive antibodies to hepatitis B core antigen (anti-HBc) total result may indicate recent, past/resolved, or chronic hepatitis B viral (HBV) infection. Testing for anti-HBc IgM (HBIM / Hepatitis B Core Antibody, IgM, Serum) is necessary to confirm the presence of acute or recent hepatitis B. A positive anti-HBc total result with a negative anti-HBc IgM result indicates past or chronic HBV infection. Differentiation between past/resolved and chronic hepatitis B can be based on the presence of hepatitis B surface antigen (HBsAg) in the latter condition. Negative anti-HBc total results indicate the absence of recent, past/resolved, or chronic hepatitis B. An inconclusive result for HBc total suggests presence of interfering substance in the patient's serum specimen. Positive antibodies to anti-HBc total results with negative anti-HBc IgM results in infants younger than 18 months may be due to passively acquired maternal IgG antibodies. Additional testing, such as HBsAg, anti-HBc IgM, and hepatitis Be antigen, are necessary to confirm a diagnosis of acute or recent hepatitis B in these infants.

**Reference Values:**

Negative

Interpretation depends on clinical setting.

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**


**Hepatitis B e Antibody, Serum**

**Clinical Information:** During recovery from acute hepatitis B, the hepatitis B e antigen (HBeAg) level declines and becomes undetectable and hepatitis B e antibody (anti-HBe) appears in the serum. Anti-HBe usually remains detectable for several years after recovery from acute infection. In hepatitis B virus (HBV) carriers and in patients with chronic hepatitis B, positive anti-HBe results usually indicate
inactivity of the virus and low infectivity of the patients. Positive anti-HBe results in the presence of detectable HBV DNA in serum indicate active viral replication. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles

**Useful For:** Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of individuals with chronic hepatitis B Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy Determining the level of hepatitis B e antibody

**Interpretation:** Absence of hepatitis B e antigen (HBeAg) with appearance of HBe antibody (anti-HBe) is consistent with inactivity of the virus and loss of hepatitis B virus (HBV) infectivity. Although resolution of chronic HBV infection generally follows the appearance of anti-HBe, the HBV carrier state may persist.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

**HEAG**

**Hepatitis B e Antigen and Hepatitis B e Antibody, Serum**

**Clinical Information:** Hepatitis B e antigen (HBeAg) is a small polypeptide that exists in a free form in the serum of individuals during the early phase of hepatitis B infection, soon after hepatitis B surface antigen (HBsAg) becomes detectable. Serum levels of both HBeAg and HBsAg rise rapidly during the period of viral replication. The presence of HBeAg in serum correlates with hepatitis B virus (HBV) infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. During recovery from acute hepatitis B, HBeAg level declines and becomes undetectable in the serum, while hepatitis B e antibody (anti-HBe) appears and becomes detectable in the serum. Anti-HBe usually remains detectable for many years after recovery from acute HBV infection. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or no HBV replication. Positive anti-HBe results usually indicate inactivity of the virus and low infectivity. Positive anti-HBe results in the presence of detectable HBV DNA in serum also indicate active viral replication in these patients.

**Useful For:** Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of individuals with chronic hepatitis B Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy Determining the levels of both hepatitis B e antigen and antibody

**Interpretation:** Presence of hepatitis B e antigen (HBeAg) and absence of HBe antibody (anti-HBe) usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBeAg with appearance of anti-HBe is consistent with loss of HBV infectivity. Although resolution of chronic HBV infection generally follows the appearance of anti-HBe, the HBV carrier state may persist.
Hepatitis B e Antigen, Serum

**Clinical Information:** Hepatitis Be antigen (HBeAg) is found in the early phase of hepatitis B infection soon after hepatitis B surface antigen becomes detectable. Serum levels of both antigens rise rapidly during the period of viral replication. The presence of HBeAg correlates with hepatitis B virus (HBV) infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or no HBV replication. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles

**Useful For:** Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of individuals with chronic hepatitis B Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy Determining the level of hepatitis Be antigen

**Interpretation:** Presence of hepatitis Be antigen (HBeAg) and absence of HBe antibody (anti-HBe) usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBeAg with appearance of anti-HBe is consistent with loss of HBV infectivity.

**Reference Values:**
Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.

Hepatitis B Perinatal Exposure Follow-up Panel, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic; others may develop chronic liver disease including cirrhosis and hepatocellular carcinoma. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen (HBsAg) carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy. Without postexposure prophylaxis (a combination of HBV vaccination and hepatitis B immune globulin), the risk of an infant acquiring HBV from an infected mother as a result of perinatal exposure is 70% to 90% for infants born to mothers who are positive for HBsAg and hepatitis B e antigen (HBeAg). The risk is 5% to 20% for infants born to HBsAg-positive but HBeAg-negative mothers. HBV is also spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles by drug addicts). The virus is found in virtually every type of human body fluid and also is spread through oral and genital contact. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles

Useful For: Determining hepatitis B virus infection and immunity status (with or without perinatal prophylaxis) in infants born to mothers with chronic hepatitis B

Interpretation: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in blood 6 to 16 weeks after exposure to HBV. A confirmed positive HBsAg result is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6-months duration indicates development of either a chronic carrier state or chronic hepatitis B. Hepatitis B surface antibody (HBsAb) appears with the resolution of HBV infection and disappearance of HBsAg. A positive result indicates recovery from acute or chronic hepatitis B, or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and recovery from HBV infection. Per assay manufacturer’s instructions for use, positive results are defined as HBsAb levels of 12.0 mIU/mL or greater, with adequate immunity to hepatitis B after recovery from past infection or HBV vaccination. Per current CDC guidance, individuals with HBsAb levels of 10 mIU/mL or greater after completing an HBV vaccination series are considered protected from hepatitis B.(1) Negative results, defined as HBsAb levels of less than 5.0 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. Indeterminate results, defined as HBsAb levels in the range of 5.0 to 11.9 mIU/mL, indicate inability to determine if HBsAb is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 3 months. Hepatitis B core (HBc) total antibodies (combined IgG and IgM) appear shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to HBV. A positive result indicates exposure to HBV infection. A positive HBsAb result along with a positive HBc total antibody result is indicative of recovery from HBV infection. A positive HBsAb result with a negative HBc total antibody result is consistent with immunity to hepatitis B from HBV vaccination. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

Clinical References: 1. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention (CDC). Immunization of health-care personnel: recommendations of the
perioperative and early posttransplant periods could delay or prevent recurrent HBV infection in these transplant recipients. Intravenous or intramuscular administration of HBIG has become the standard of care for these liver transplant recipients in most liver transplant programs in the United States since mid-1990. Most therapy protocols administer HBIG in high doses (10,000 IU) during the perioperative period and first week after transplantation, with the goal of achieving serum hepatitis B surface antibody (anti-HBs) levels of above 500 mIU/mL. Serial levels of anti-HBs are obtained to determine the pharmacokinetics of HBIG in each patient to guide frequency of HBIG dosing. There is a high degree of variability in HBIG dosage required to achieve desirable serum anti-HBs levels among transplant recipients during the first few weeks to months after transplantation. Patients who were hepatitis B e (HBe) antigen positive before transplantation usually require more HBIG to achieve the target anti-HBs levels, especially in the first week after transplantation. Duration of HBIG therapy varies from 6 months to indefinite among different US liver transplant programs. Protocols providing less than 12 months of therapy usually combine HBIG with another effective anti-HBV agent such as lamivudine. See HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

**Useful For:** Monitoring serum anti-hepatitis B surface (anti-HBs) levels during intravenous or intramuscular hepatitis B immune globulin (HBIG) therapy to prevent hepatitis B virus (HBV) reinfection in liver transplant recipients with known previous chronic HBV

**Interpretation:** Please refer to health care provider's institutional hepatitis B immune globulin (HBIG) therapy protocol for desirable hepatitis B surface antibody (anti-HBs) levels. Studies indicated that serum anti-HBs levels needed to prevent hepatitis B virus (HBV) reinfection were greater than 500 mIU/mL during the first week after transplantation, greater than 250 mIU/mL during weeks 2 to 12, and greater than 100 mIU/mL after week 12. See HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

**Reference Values:**
Not applicable

**Clinical References:**
age and in 5% to 10% of infected individuals age 5 or older. Some of these chronic carriers are asymptomatic, while others progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) is the first serologic marker, appearing in the serum 6 to 16 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms with the appearance of hepatitis B surface antibody (anti-HBs). Anti-HBs also appears as the immune response following hepatitis B vaccination. See HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions

**Useful For:** Identifying previous exposure to hepatitis B virus
Determining adequate immunity from hepatitis B vaccination

**Interpretation:** A positive result indicates recovery from acute or chronic hepatitis B virus (HBV) infection or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and an immune response induced by infection with HBV. A positive total antihepatitis B core (anti-HBc) result would indicate that the hepatitis B surface antibody (anti-HBs) response is due to past HBV infection. Per assay manufacturer's instructions for use, positive results, defined as anti-HBs levels of 12.0 mIU/mL or greater, indicate adequate immunity to hepatitis B from past hepatitis B or HBV vaccination. However, per current CDC guidance, individuals with anti-HBs levels greater than 10 mIU/mL after completing an HBV vaccination series are considered protected from hepatitis B. Negative results, defined as anti-HBs levels of less than 5.0 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B virus or inadequate immune response to HBV vaccination. The US Advisory Committee on Immunization Practices does not recommend more than 2 HBV vaccine series in nonresponders. Indeterminate results, defined as anti-HBs levels in the range from 5 to 11.9 mIU/mL, indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 3 months. See HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions.

**Reference Values:**

**HEPATITIS B SURFACE ANTIBODY**
- Unvaccinated: negative
- Vaccinated: positive

**HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE**
- Unvaccinated: <5.0 mIU/mL
- Vaccinated: > or =12.0 mIU/mL

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**
**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles

**Useful For:** Diagnosis of acute, recent, or chronic hepatitis B infection in prenatal patients. This test is not useful during the "window period" of acute hepatitis B virus (HBV) infection (i.e., after disappearance of HBsAg and prior to appearance of hepatitis B surface antibody: anti-HBs). This test is not suitable as a stand-alone prenatal screening test of HBsAg status in pregnant women. This test is not offered as a hepatitis B surface antigen (HBsAg) screening or confirmatory test for blood donor specimens.

**Interpretation:** A reactive screen result (signal-to-cutoff ratio ≥ 1.00, but < 100.0) confirmed as positive by a hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B virus (HBV) infection or chronic HBV carrier state. Specimens with reactive screen results but negative (i.e., not confirmed) HBsAg confirmatory test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. Repeat testing is recommended at a later date if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B envelope (HBe) antigen and/or detectable HBV DNA. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles

**Reference Values:** Only orderable as a reflex. For more information see HBAGP / Hepatitis B Surface Antigen Prenatal, Serum.

**Negative**

sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following HBV infection. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for greater than 6 months indicates development of either a chronic carrier or chronic HBV infection.

**Useful For:** Testing cadaveric and hemolyzed blood specimens for hepatitis B surface antigen (HBsAg); FDA-licensed for use with hemolyzed specimens Diagnosis of acute, recent (<6 month duration), or chronic hepatitis B infection; determination of chronic hepatitis B carrier status This test is not useful during the "window period" of acute hepatitis B virus (HBV) infection, (ie, after disappearance of HBsAg and prior to appearance of anti-HBs antibody).

**Interpretation:** A positive result (reactive screening and confirmed positive by neutralization test) is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. A positive confirmatory test result is considered the definitive test result for hepatitis B surface antigen (HBsAg). Specimens that are reactive by the screening test but negative (not confirmed) by the confirmatory test are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg screening test results should be interpreted in conjunction with test results of other HBV serological markers (eg, anti-hepatitis B surface antibody, anti-hepatitis B core total antibody). The presence of HBsAg is frequently associated with HBV infectivity, especially when accompanied by the presence of hepatitis Be antigen or HBV DNA.

**Reference Values:**
Negative

**Clinical References:**
HBAG

Hepatitis B Surface Antigen, Serum

Clinical Information: Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation

Useful For: Diagnosis of acute, recent, or chronic hepatitis B infection Determination of chronic hepatitis B infection status This test is not offered as a screening or confirmatory test for blood donor specimens. This test, by itself, is not useful during the "window period" of acute hepatitis B virus (HBV) infection (ie, after disappearance of hepatitis B surface antigen and prior to appearance of hepatitis B surface antibody ). Testing for acute HBV infection should also include hepatitis B core IgM antibody (anti-HBe IgM).

Interpretation: A reactive screen result (signal-to-cutoff ratio [S/Co]: > or =1.00, but < or =100.0) confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test (see Method Description) or a positive screen result (S/Co >100.0) is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with initially reactive screen results, but negative (not confirmed) by HBsAg confirmatory test results, are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg-reactive screening test results should be interpreted in conjunction with test results of other HBV serologic markers (eg, hepatitis B surface antibody; hepatitis B core antibody, total and IgM). Repeat testing is recommended at a later date if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B e antigen and/or detectable HBV DNA. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles
Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.


HBVQN 65555

Hepatitis B Virus (HBV) DNA Detection and Quantification by Real-Time PCR, Serum

Clinical Information: Diagnosis of acute or chronic hepatitis B virus (HBV) infection is based on the presence of HBV serologic markers such as hepatitis B surface antigen (HBsAg) and hepatitis B core IgM antibody (anti-HBc IgM), or the presence of HBV DNA detected by molecular assays. Although the diagnosis of acute and chronic HBV infection is usually made by serologic methods, detection and quantification of HBV DNA in serum are useful for: - Diagnose some cases of early acute HBV infection (before the appearance of HBsAg) - Distinguish active from inactive HBV infection - Monitor a patient's response to anti-HBV therapy The presence of HBV DNA in serum is a reliable marker of active HBV replication. HBV DNA levels are detectable by 30 days following infection, generally reach a peak at the time of acute hepatitis, and gradually decrease and disappear when the infection resolves spontaneously. In cases of acute viral hepatitis with equivocal HBsAg test results, testing for HBV DNA in serum may be a useful adjunct in the diagnosis of acute HBV infection, since HBV DNA can be detected approximately 21 days before HBsAg typically appears in the serum. Patients with chronic HBV infection fail to clear the virus and remain HBsAg-positive. Such cases may be further classified as chronic active (replicative) HBV (high HBV levels, hepatitis Be antigen [HBeAg]-positive) or chronic inactive (nonreplicative) HBV (low or undetectable HBV DNA levels, HBeAg-negative). HBV DNA levels in serum are useful in determining the status of chronic HBV infection, by differentiating between active and inactive disease states. Patients with chronic active HBV are at greater risk for more serious liver disease and are more infectious than patients with inactive HBV infection. Reactivation of inactive chronic HBV infection (HBeAg-negative state) may occur with or without reappearance of HBeAg in serum. In patients with HBeAg-negative disease, detection of HBV DNA is the only reliable marker of active HBV replication. The therapeutic goal of anti-HBV therapy in patients who are HBeAg-positive is to achieve long-term suppression of viral replication with undetectable HBV DNA, HBe seroconversion and loss of HBeAg. The therapeutic goal in patients with HBeAg-negative disease is typically long-term viral suppression. The emergence of drug-resistant HBV strains in response to treatment with nucleoside/nucleotide analogs (eg, lamivudine, adefovir, entecavir, tenofovir), is characterized by either the reappearance of HBV DNA in serum (after it had become undetectable) or an increase in HBV DNA levels (following an initial decline). The following algorithms are available in Special Instructions: - HBV Infection-Diagnostic Approach and Management Algorithm - HBV Infection-Monitoring Before and After Liver Transplantation

Useful For: Detection and quantification of hepatitis B virus (HBV) DNA in serum of patients with chronic HBV infection (ie, hepatitis B surface antigen-positive) Monitoring disease progression in chronic HBV infection Monitoring response to anti-HBV therapy
**Interpretation:** The quantification range of this assay is 10 to 1,000,000,000 IU/mL (1.00 log to 9.00 log IU/mL). An "Undetected" result indicates that hepatitis B virus (HBV) DNA was not detected in the serum specimen. A result of "<10 IU/mL (<1.00 log IU/mL)" indicates that HBV DNA is detected, but the HBV DNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HBV viral replication in the patient. Monitoring HBV DNA levels over time is important for assessing disease progression or monitoring a patient's response to anti-HBV therapy. A result of ">1,000,000,000 IU/mL (>9.00 log IU/mL)" indicates the presence of active HBV viral replication, and the HBV DNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result with the comment "Submit a new specimen for testing if clinically indicated" indicates that inhibitory substances may be present in the specimen. When clinically indicated, collection and testing of a new specimen is recommended.

**Reference Values:**

Undetected

**Clinical References:**

**Hepatitis B Virus Genotyping**

**Reference Values:**

Interpretive Information: Hepatitis B Virus Genotype

HBV genotype and resistance interpretation is provided by SeqHepB software from Evivar Medical. The following mutations are reported: reverse transcriptase L80I/V, I69T, V173L, L180M, A181S/T/V, T184A/C/F/I/G/S/M/L, S202C/G/I, M204I/V, N236T, M250I/L/V; surface antigen P120T, D144A, G145R.

Both the HBV RT polymerase and the HBsAg encoding regions are sequenced. Resistance and surface antigen mutations are reported. In addition, the major HBV genotypes are identified. Mutations in viral sub-populations below 20% of total may not be detected.

This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.

**Hepatitis B Virus Past Exposure Panel, Serum**

**Clinical Information:** Hepatitis B is a DNA viral infection that is endemic throughout the world. The hepatitis B virus (HBV) is transmitted parenterally or percutaneously from exposure to contaminated blood, blood products, or injection needles, sexually from exposure to body fluids from infected individuals, or perinatally from mother to child during birth delivery by contact with infected mother's blood and vaginal secretions. Transplacental transmission from mother to fetus is uncommon. HBV persists and causes chronic infection (defined as being positive for hepatitis B virus surface antigen: HBsAg in serum or plasma for minimum 6 months) in about 10% of individuals who had acute infection during childhood. These individuals may become asymptomatic HBV carriers (ie, inactive chronic hepatitis B), while others may develop chronic liver diseases including cirrhosis and hepatocellular carcinoma. Asymptomatic HBV carriers are at risk (up to 50%) for decompensation of
liver function with acute HBV replication (ie, HBV reactivation) during immunosuppression from chemotherapy, immunosuppressive therapy, or organ transplantation. Individuals who recovered from acute hepatitis B (defined as being negative for HBsAg, positive for total HBV core antibodies, negative or positive for HBV virus surface antibody) are lower risk (up to 20%) of HBV reactivation than those with inactive chronic hepatitis B during immunosuppressive therapy or organ transplantation. For individuals born in regions of the world where HBV prevalence is moderate to high, universal HBV serologic screening before initiation of immunosuppressive therapy is recommended. In the absence of systematic, risk-based testing, universal HBV serologic screening is an option to reduce the risk of missing persons with HBV infection prior to initiation of immunosuppressive treatment.

**Useful For:** Screening for past exposure to hepatitis B virus (HBV) Determining HBV infection status prior to initiating chemotherapy or other immunosuppressive therapies

**Interpretation:** Hepatitis B virus surface antigen (HBsAg) is the first serologic marker appearing in blood 6 to 16 weeks after exposure to hepatitis B virus (HBV). A confirmed positive HBsAg result is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6-months duration indicates development of either a chronic carrier state or chronic hepatitis B. Hepatitis B virus surface antibody (HBsAb) appears with the resolution of HBV infection and disappearance of HBsAg. A positive result indicates recovery from acute or chronic hepatitis B or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and recovery from HBV infection. Per assay manufacturer’s instructions for use, positive results are defined as HBsAb levels of 12.0 mIU/mL or greater, with adequate immunity to hepatitis B after recovery from past infection or HBV vaccination. Per current CDC guidance, individuals with HBsAb levels of 10 mIU/mL or greater after completing an HBV vaccination series are considered protected from hepatitis B. Negative HBsAb results (levels of < 5.0 mIU/mL) indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. Indeterminate results, defined as HBsAb levels in the range of 5.0 to 11.9 mIU/mL, indicate inability to determine if HBsAb is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 3 months. Hepatitis B virus core (HBc) total antibodies (combined IgG and IgM) appear shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to HBV. A positive result indicates exposure to HBV infection. A positive HBsAb result along with a positive HBC total Ab result is indicative of recovery from HBV infection. A positive HBsAb result with a negative HBC total Ab result is consistent with immunity to hepatitis B from HBV vaccination. Summary of interpretation of the various HBV serologic test result profiles is provided in the table below: HBV serologic test results Interpretation HBsAg Hbc total Ab HBs Ab + + - Chronic hepatitis B + + Past HBV infection (resolved) + - Past HBV infection, resolved or false-positive - - + Immune (from HBV vaccination) - - - Uninfected (not immune)

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

**Hepatitis C Viral RNA Genotype 1 NS5a Drug Resistance**

**Clinical Information:** The clinical significance of NS5a resistance associated variants for antiviral therapy may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient. Testing for NS5a resistance-associated variants prior to initiation of treatment with elbasvir plus grazoprevir in HCV genotype 1a infected patients is recommended.

**Reference Values:**
**Hepatitis C Virus (HCV) Antibody Screen Prenatal, Serum**

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-polymerase chain reaction (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur following resolution of infection. Current screening serologic tests to detect antibodies to HCV include enzyme and chemiluminescence immunoassays. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as a nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. See Hepatitis C: Testing Algorithm for Screening and Diagnosis in Special Instructions.

**Useful For:** Screening of pregnant women for hepatitis C in primary care settings, with or without risk factors for hepatitis C. This test should not be used as a screening test for hepatitis C in blood or human cells/tissue donors. This test profile is not useful for detection or diagnosis of acute hepatitis C virus (HCV), since HCV antibodies may not be detectable until after 2 months following exposure and HCV RNA testing is not performed on specimens with negative HCV antibody screening test results.

**Interpretation:** Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/CO) ratios of below 8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm HCV antibody status. Reactive results with S/CO ratios of 8.0 or greater are highly predictive (95% or greater probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVRP / Hepatitis C Virus (HCV) RNA Detection and Quantification, Real-Time Reverse Transcription-PCR Prenatal, Serum is recommended for detection of HCV infection in such patients.

**Reference Values:**
- Negative
  - See Viral Hepatitis Serologic Profiles in Special Instructions.

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**Hepatitis C Viral RNA Genotype 3 NS5a Drug Resistance**

**Clinical Information:** The clinical significance for antiviral therapy of NS5a resistance associated variants may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient.

**Reference Values:**
- HCV NS5a Subtype: Not Detected

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**HCV NS5a Subtype: ** Not Detected

**FH3N5 75188**

**Hepatitis C Viral RNA Genotype 3 NS5a Drug Resistance**

**Clinical Information:** The clinical significance for antiviral therapy of NS5a resistance associated variants may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient.

**Reference Values:**
- HCV NS5a Subtype: Not Predicted

HCSRN

Hepatitis C Virus (HCV) Antibody Screen with Reflex to HCV RNA, PCR, Asymptomatic, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-PCR (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur following resolution of infection. Current screening serologic tests to detect antibodies to HCV include enzyme immunoassay (EIA) and chemiluminescence immunoassays (CIA). Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as a nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide very sensitive and specific approach for the direct detection of HCV RNA. See Hepatitis C: Testing Algorithm for Screening and Diagnosis in Special Instructions.

Useful For: Screening for hepatitis C in primary care settings in high-risk persons with a current or past history of illicit injection drug use or a history of receiving a blood transfusion prior to 1992 Screening for hepatitis C in primary care settings in non-high risk persons born from 1945 through 1965 Screening at least once in a lifetime for all adults greater or equal to 18 years old, except in settings where the prevalence of HCV infection is less than 0.1% This test is not offered as a screening or confirmatory test for hepatitis C in blood or human cells/tissue donors. This test profile is not useful for detection or diagnosis of acute hepatitis C virus (HCV), since HCV antibodies may not be detectable until after 2 months following exposure and HCV RNA testing is not performed on specimens with negative HCV antibody screening test results.

Interpretation: Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/Co) ratios of below 8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm HCV antibody status. Reactive results with S/Co ratios of 8.0 or greater are highly predictive (95% or greater probability) of the true HCV antibody status but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in
Hepatitis C Virus (HCV) Antibody with Reflex to HCV RNA, PCR, Symptomatic, Serum

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-PCR (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur after resolution of infection. Current screening serologic tests to detect antibodies to HCV include enzyme immunoassay (EIA) and chemiluminescence immunoassay (CIA). Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of a detectable HCV antibody. -False-reactive screening test result can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to anti-HCV therapy. Reactive screening test results should be followed by a supplemental or confirmatory test, such as nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. See Hepatitis C: Testing Algorithm for Screening and Diagnosis in Special Instructions.

**Useful For:** Diagnosis of recent or chronic hepatitis C virus infection in symptomatic patients. This test is not offered as a screening or confirmatory test for hepatitis C virus (HCV) for blood, human cells, or tissue donors. This test profile is not useful for detection or diagnosis of acute HCV, since HCV antibodies may not be detectable until after 2 months following exposure and HCV RNA testing is not performed on specimens with negative anti-HCV screening test results.

**Interpretation:** Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/Co) ratios of below 8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm anti-HCV status. Reactive results with S/Co ratios of 8.0 or greater are highly predictive (95% or greater probability) of the true anti-HCV status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody.
results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum is recommended for detection of HCV infection in such patients.

**Reference Values:**

Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.


**HCVQN**

**Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum**

**Clinical Information:** Of all individuals infected with hepatitis C virus (HCV), about 75% of them will develop chronic hepatitis C, with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the infected individuals. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24 to 48 week duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy now. Cure rates, as defined by sustained virologic response (SVR), of over 90% are observed among HCV-infected patients treated with interferon-free DAA combinations that are of shorter duration of treatment (eg, 8 or 12 weeks) than those of interferon-based therapy. Current guidelines for antiviral therapy of chronic hepatitis C recommend quantitative testing for HCV RNA in serum or plasma before initiating antiviral therapy, at 4 weeks of therapy, and at 12 weeks after completion of therapy. HCV RNA level of below 25 IU/mL in serum or plasma at 12 weeks after ending therapy is the therapeutic goal and indicates an SVR is achieved. Quantitative HCV RNA testing can be considered at the end of therapy and at 24 weeks or later after completion of antiviral therapy. The following algorithms are available in Special Instructions: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis C: Testing Algorithm for Screening and Diagnosis

**Useful For:** Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive) Monitoring disease progression in chronic HCV infection and response to antiviral therapy Determining cure and detection of relapse after completion of antiviral therapy

**Interpretation:** This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. To assess response-guided therapy eligibility, an "Undetected" result is
required, and a result of "<15 IU/mL mL (<1.18 log IU/mL)" should not be considered equivalent to an "Undetected" result. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HCV viral replication in the patient. Monitoring HCV RNA levels over time is important to assess disease progression and/or monitoring a patient's response to anti-HCV therapy. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting.

Reference Values:
Undetected

Clinical References:

**Hepatitis C Virus (HCV) RNA Detection and Quantification, Real-Time Reverse Transcription-PCR, Prenatal, Serum**

**Clinical Information:** Of all individuals infected with hepatitis C virus (HCV), about 75% of them will develop chronic hepatitis C, with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the individuals infected recover from the infection without evidence of viral replication or presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the individuals infected. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24 to 48 weeks duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy now. Cure rates, as defined by sustained virologic response (SVR), of over 90% are observed among HCV-infected patients treated with interferon-free DAA combinations that are of shorter duration of treatment (eg, 8 or 12 weeks) than those of interferon-based therapy. Current guidelines for antiviral therapy of chronic hepatitis C recommend quantitative testing for HCV RNA in serum or plasma before initiating antiviral therapy, at 4 weeks of therapy, and at 12 weeks after completion of therapy. HCV RNA level of below 25 IU/mL in serum or plasma at 12 weeks after ending therapy is the therapeutic goal and indicates an SVR is achieved. Quantitative HCV RNA testing can be considered at the end of therapy and at 24 weeks or later after completion of antiviral therapy. The following algorithms are available in Special Instructions: Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis C: Testing Algorithm for Screening and Diagnosis

**Useful For:** Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) in women who are pregnant Detection and confirmation of chronic HCV infection in women who are pregnant Quantification of HCV RNA in serum of women who are pregnant for monitoring disease progression of chronic HCV infection (HCV...
**Interpretation:** This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. To assess response-guided therapy eligibility, an "Undetected" result is required, and a result of "<15 IU/mL mL (<1.18 log IU/mL)" should not be considered equivalent to an "Undetected" result. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HCV viral replication in the patient. Monitoring HCV RNA levels over time is important to assess disease progression and/or monitoring a patient's response to anti-HCV therapy. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting.

**Reference Values:**

**Undetected**

**Clinical References:**


**Hepatitis C Virus (HCV) RNA Quantification with Reflex to HCV Genotype, Serum**

**Clinical Information:** Of all individuals infected with hepatitis C virus (HCV), about 75% of them will develop chronic hepatitis C, with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or the presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the infected individuals. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24 to 48 week duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy now. Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the HCV genome allow classification of HCV into 6 major genotypes or clades (1-6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most commonly encountered HCV genotypes are 1a and
1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. HCV genotype determination is important for proper selection of antiviral therapy and optimal patient management. Therapeutic response rates for chronic HCV infection have improved significantly (cure rates of >90%) over the past 5 years when oral DAA agents are used in lieu of interferon-based combination therapy. However, antiviral resistance can emerge during such combination therapy, and occurrence of such resistance is more frequent with HCV subtype 1a than 1b for simeprevir-treated patients. The American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C are available at www.hcvguidelines.org/full-report-view.

**Useful For:** Detection of acute HCV infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection, and determining HCV genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive) before initiating antiviral therapy Determining cure and detection of relapse of HCV infection after completion of antiviral therapy

**Interpretation:** This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. Only those specimens with HCV RNA levels of greater than or equal to 500 IU/mL will be tested for HCV genotype (HCVG / Hepatitis C Virus Genotype, Serum or HCVGR / Hepatitis C Virus Genotype Resolution, Serum). An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. Such specimens will not be tested for HCV genotype. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. Such specimens will not be tested for HCV genotype. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting. Such specimens will not be tested for HCV genotype.

**Reference Values:**
Undetected


**Hepatitis C Virus Antibody Confirmation, Serum**

**Clinical Information:** Laboratory testing for hepatitis C virus (HCV) infection in patients and donors of organ, blood, cells, tissue, and tissue products usually begins by screening for the presence of HCV antibodies (anti-HCV) in serum, using an FDA-approved anti-HCV screening test. Specimens that are repeatedly reactive by screening tests should be confirmed by more HCV-specific tests, such as direct detection of HCV RNA by the reverse transcriptase-polymerase chain reaction (RT-PCR) assay or confirmatory detection of HCV antibodies by serologic assays using recombinant HCV-specific antigens. In patients with reactive HCV antibody screening test results but negative or undetectable HCV RNA test results, HCV antibody confirmatory tests would be useful to distinguish between true- and false-reactive HCV antibody screening test results. HCV antibodies are usually not detectable during the first 2 months following infection, and they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur in the years following resolution of infection. Despite the value of serologic confirmation of HCV infection, several limitations of this test exist: -There may be a long delay (up to 6 months) between exposure to the virus
and development of detectable HCV antibodies, especially in immunocompromised patients. A positive test result does not distinguish between past (resolved) and chronic HCV infection. Serologic tests cannot predict or monitor response to antiviral therapy. See Hepatitis C: Testing Algorithm for Screening and Diagnosis in Special Instructions.

**Useful For:** Confirming the presence of hepatitis C virus (HCV)-specific IgG antibodies in serum specimens that are reactive by HCV antibody screening tests. Distinguishing between true- and false-reactive HCV antibody screening test results. This test is not intended for use as an HCV antibody screening test for blood or human cells/tissue donors. This assay is not useful for detection of early or acute hepatitis C (<2 months from exposure) as immunocompromised patients may not develop detectable HCV antibodies in blood until 6 months after infection. This assay is not useful for differentiating between past (resolved) and chronic hepatitis C.

**Interpretation:** A positive result indicates the presence of hepatitis C virus (HCV)-specific IgG antibodies due to past (resolved) or chronic hepatitis C. Past (resolved) HCV infection (accounting for about 25% of all HCV-infected patients) can be distinguished from chronic HCV infection (about 75% of all cases) only by direct detection of HCV RNA using molecular test methods; e.g., HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum. HCV RNA is present in acute or chronic hepatitis C but not in past (resolved) HCV infection. A negative result indicates the absence of HCV-specific IgG antibodies. A reactive HCV antibody screening test result with a negative HCV antibody confirmatory result indicates a probable false-reactive screening test result. An indeterminate result indicates that HCV-specific IgG antibodies may or may not be present. Indeterminate results should be interpreted along with patient's risk factors for HCV infection and clinical findings. Individuals at risk for HCV infection with indeterminate results should be retested with an HCV antibody confirmatory test in 1 to 2 months to determine the definitive HCV antibody status. Molecular tests to detect HCV RNA may be necessary to determine HCV infection status in those at-risk immunocompromised patients with indeterminate HCV antibody confirmatory test results due to delayed appearance of fully complement of HCV-specific antibodies. An unreadable result indicates nonspecific cross reactivity was present and HCV-specific antibody bands could not be visualized reliably. Repeat confirmatory serologic testing in 1 to 2 months or HCV RNA (HCVQN / Hepatitis C Virus [HCV] RNA Detection and Quantification by Real-Time Reverse Transcription-PCR [RT-PCR], Serum) is recommended for at-risk patients.

**Reference Values:**
- **Negative**

**Clinical References:**

**Hepatitis C Virus Antibody in Cadaveric or Hemolyzed Specimens, Symptomatic, Serum**

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronic HCV carriers. HCV antibodies are usually not detectable during the early months following infection, but they are almost always detectable by the late convalescent stage (>6 months after onset of acute infection). These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic
tests to screen for HCV infection, several limitations of serologic testing are known: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. -False-reactive screening test results can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric blood specimens due to interference of heme with the nucleic acid amplification processes.

**Useful For:** Diagnosis of hepatitis C virus (HCV) infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HCV infection. This test is not intended for screening blood, cell, or tissue donors. This test is not useful for ruling out acute HCV infections. This test is not useful for differentiation between resolved and acute or chronic hepatitis C infections. This test is not intended for testing asymptomatic individuals (ie, screening purposes).

**Interpretation:** All specimens with signal-to-cutoff ratios of 1.0 or greater will be considered reactive and reflex to the hepatitis C virus (HCV) antibody confirmatory test by line immunoassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

**Reference Values:**
Negative

**Clinical References:**
infection in asymptomatic individuals with or without risk factors for HCV infection. Note: In accordance with National Coverage Determination guidance, this test is indicated for asymptomatic patients born from 1945 through 1965, those with history of injection drug use, or history of receiving blood transfusion prior to 1992. This test is not intended for screening blood, cell, or tissue donors. This test is not intended for testing symptomatic individuals (ie, diagnostic purposes). This test is not useful for ruling out acute HCV infection. This test is not useful for differentiation between resolved and acute or chronic HCV infection.

**Interpretation:** All specimens with signal-to-cutoff ratios of 1.0 or greater will be considered reactive and reflex to the hepatitis C virus (HCV) antibody confirmatory test by line immunosassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

**Reference Values:**

Negative

**Clinical References:**


**HCVG 81618**

**Hepatitis C Virus Genotype, Serum**

**Clinical Information:** Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the hepatitis C virus (HCV) genome allow classification of HCV into 6 major genotypes or clades (1-6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most commonly encountered HCV genotypes are 1a and 1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. Therefore, reliable methods for genotype determination are important for proper selection of antiviral therapy and optimal patient management. Infections with HCV genotypes 2 and 3 have better therapeutic response rates (80%-90%) than genotypes 1 and 4 (40%-50%) to previous standard combination therapy (ribavirin plus pegylated interferon alpha-2a or alpha-2b). Duration of such combination therapy is 24 weeks for chronic HCV genotype 2 and 3 infections in patients who show early virologic response (>2 log or 100-fold decrease in HCV RNA or no detectable HCV RNA at week 12 of therapy), while patients with chronic HCV genotype 1 and 4 infections receive a minimum of 48 weeks of such combination therapy if early virologic response is achieved (undetectable HCV RNA at week 4 of therapy). Therapeutic response rates for HCV genotype 1 infection are improved significantly (80%-90%) when oral direct acting antiviral agents (eg, daclatasvir, sofosbuvir, ledipasvir + sofosbuvir, velpatasvir + sofosbuvir, glecaprevir + pibrentasvir, elbasvir + grazoprevir, velpatasvir + voxilaprevir + sofosbuvir) are added or used in lieu of interferon-based combination therapy. The American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C are available at www.hcvguidelines.org/full-report-view The following algorithms are available in Special Instructions: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis C: Testing Algorithm for Screening and Diagnosis

**Useful For:** Determining hepatitis C virus (HCV) genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Differentiating between HCV subtypes 1a and 1b This assay should not be used as a screening test for HCV infection. It should be performed only on specimens obtained from patients confirmed to have HCV RNA levels in serum of 500 IU/mL or higher.

**Interpretation:** An "Undetected" result indicates the absence of detectable hepatitis C virus (HCV)
RNA in the specimen. An "Indeterminate" result may be due to 1 or more of the following causes: 1) low HCV RNA level (ie, <500 IU/mL), 2) HCV genotype 6, 3) probe reactivity with multiple HCV genotypes, or 4) variation in patient's HCV target sequences with mismatches to PCR primers and/or probes. Specimens generating indeterminate results with this assay will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum. An HCV genotype result of "1" without a subtype result may be due to 1 or more of the following causes: 1) low HCV RNA level (ie, <500 IU/mL), 2) probe reactivity with multiple genotype 1 subtypes, 3) variation in HCV genotype 1 target sequence, or 4) misclassification of some true genotype 6 strains. This assay is able to differentiate between HCV subtypes 1a and 1b. However, subtypes are not reported for HCV genotypes 2 to 5 due to limitations of the current genotyping assay in accurately differentiating the various subtypes of these genotypes. Results with multiple or mixed HCV genotypes (eg, 1, 5; 1a, 2; or 3, 5) may be due to mixed genotype infection or assay probe cross-reactivity. Only those specimens with multiple or mixed genotype results containing genotype 1 but no subtype will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum.

Reference Values:
Undetected


AHDV 9209

Hepatitis D Virus Total Antibodies, Serum

Clinical Information: Hepatitis D virus (HDV), also known as delta hepatitis virus, is a defective RNA virus comprised of a delta antigen and a hepatitis B surface antigen (HBsAg) as the core and protein coat of the virus, respectively. This virus cannot replicate effectively by itself as it requires the presence of hepatitis B virus (HBV) to initiate and maintain its replication in the infected liver cells. Infection with HDV occurs either as an acute coinfection with HBV or an acute superinfection of chronic HBV. Acute HBV-HDV coinfection usually follows a self-limited clinical course with spontaneous resolution but may have a fulminant clinical presentation. HDV superinfection in chronic HBV or in HBV carrier state typically manifests as an acute exacerbation of chronic hepatitis B, with tendency to result in chronic HBV-HDV coinfection and early cirrhosis or liver failure. Chronic HDV infection is found in 1% of all chronically HBV-infected individuals in the United States. Diagnosis of HDV can be established by detecting HDV antigen, HDV-specific IgM, or HDV-specific total antibodies (combined IgM and IgG) in the sera of infected patients with clinically evident acute or chronic hepatitis B. Anti-HDV IgM typically appears in serum at 2 to 3 weeks after onset of symptoms and disappears by 2 months after acute HDV infection, but it may persist up to 9 months in HDV superinfection. HDV IgG and HDV total antibodies persist in serum after resolution of acute HDV infection and in chronic coinfection.

Useful For: Detection of hepatitis D virus (HDV)-specific total antibodies (combined IgG and IgM) in human serum Diagnosis of concurrent HDV infection in patients with fulminant acute hepatitis B virus (HBV) infection (acute coinfection), chronic HBV infection (chronic coinfection), or acute exacerbation of known chronic HBV infection (HDV superinfection)

Interpretation: This assay detects the presence of hepatitis D virus (HDV)-specific total (combined IgG and IgM) antibodies in serum. Negative results indicate the absence of HDV infection and no past exposure to HDV. Equivocal results indicate borderline level of anti-HDV total antibodies. Repeat testing in 1 to 2 weeks is recommended to determine the definitive HDV infection status. Positive results usually indicate one of the following conditions: 1) simultaneous acute or chronic coinfection with hepatitis B virus (HBV) and HDV, 2) acute HDV infection in patients with known chronic HBV infection (ie, HDV superinfection), or 3) resolved HDV infection. Results should be correlated with medical history and clinical findings. See Viral Hepatitis Serologic Profiles in Special Instructions.

Reference Values:
**HEVG 86211**

**Hepatitis E Virus IgG Antibody, Serum**

**Clinical Information:** Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, non-enveloped RNA virus is transferred from animal reservoir (eg, hogs) to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the feces. In immunocompetent patients, viremia and virus shedding in the feces occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgG is the serologic test of choice to determine past exposure to HEV.

**Useful For:** Diagnosis of past exposure to hepatitis E virus

**Interpretation:** Positive results indicate past or resolved hepatitis E infection. Negative results indicate absence of previous exposure to hepatitis E virus (HEV). Borderline results may be seen in: 1) acute or recent hepatitis E infection with rising level of anti-HEV IgG, or 2) cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status.

**Reference Values:**
Negative


**HEVML 61903**

**Hepatitis E Virus IgM Antibody Confirmation, Serum**

**Clinical Information:** Hepatitis E virus (HEV) causes an acute, usually self-limited, infection. This small, non-enveloped RNA virus is from animal reservoirs (eg, hogs) and is transmitted to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in individuals who have traveled to disease-endemic areas. Transmission of HEV may also occur rarely from direct person-to-person contact or transfusion of blood or blood products. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the stool. In immunocompetent patients, viremia and virus shedding in the stool occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection.
Positive predictive value of a given diagnostic laboratory test is dependent on the prevalence rate of the disease for which the test is being used. Screening tests for detection of diseases with low prevalence rates, such as acute hepatitis E, will have low positive predictive values (ie, relatively high rates of false-positive test results), despite having high specificity rates for such tests. Therefore, an HEV IgM antibody confirmatory test is helpful and necessary to determine the true infection status of patients with reactive HEV IgM antibody screening test results.

**Useful For:** Confirmation of reactive hepatitis E virus IgM antibody screening test results for the diagnosis of acute or recent (<6 months) hepatitis E infection

**Interpretation:** Positive results confirm the presence of acute or recent (in the preceding 6 months) hepatitis E infection. Negative results indicate absence of acute or recent hepatitis E infection. Indeterminate results may be seen in: 1) acute hepatitis E infection with rising level of anti-hepatitis E virus (HEV) IgM; 2) recent hepatitis E infection with declining level of anti-HEV IgM; 3) acute hepatitis E infection due to HEV genotype 2 strains; or 4) cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgM and anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status. Unreadable results indicate the presence of unusually strong, nonspecific reactivity of the assay strip background that obscures proper reading of the bands. Such findings are usually due to nonspecific binding of non-hepatitis E IgM antibodies in patient's serum to the HEVM antigens present on the assay strip. Repeat testing with anti-HEV IgM screen and anti-HEV IgG in 4 to 6 weeks is recommended.

**Reference Values:**

**Clinical References:**

**Hepatitis E Virus IgM Antibody Screen with Reflex to Confirmation, Serum**

**Clinical Information:** Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, non-enveloped RNA virus is transmitted from animal reservoir (eg, hogs) to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the feces. In immunocompetent patients, viremia and virus shedding in the feces occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection.

**Useful For:** Diagnosis of acute or recent (<6 months) hepatitis E infection

**Interpretation:** Positive results suggest the presence of acute or recent (in the preceding 6 months) hepatitis E infection. Negative results indicate absence of acute or recent hepatitis E infection. If clinical suspicion persists, submit new specimen for retesting in 1 to 2 weeks. Borderline results may be seen in: 1) acute hepatitis E infection with rising level of anti-hepatitis E virus (HEV) IgM; 2) recent hepatitis E infection with declining level of anti-HEV IgM; or 3) cross-reactivity with nonspecific antibodies (ie, false-positive results).

**Reference Values:**

Hepatocellular Carcinoma Risk Panel with GALAD Score, Serum

Clinical Information: Worldwide, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death.(1) While HCC can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of suspected HCC. However, increased serum concentrations of AFP might be found in chronic hepatitis and liver cirrhosis, as well as in other tumor types (eg, germ cell tumors)(2), decreasing the specificity of AFP testing for HCC. Furthermore, AFP is not expressed at high levels in all HCC patients, resulting in decreased sensitivity, especially in potentially curable small tumors. AFP-L3: AFP is differentially glycosylated in several hepatic diseases. For example, UDP-alpha-(1->6)-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation.(3) This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following electrophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP that is most closely associated with HCC is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP of 200 ng/mL or less, which may result from a variety of benign pathologies, such as chronic liver diseases. Des-gamma-carboxy prothrombin (DCP): (DCP, also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many HCC cells, and an abnormal prothrombin with all or some of unconverted glutamic acid is secreted. Therefore, this noncarboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to AFP and AFP-L3 for assessing the risk of developing HCC. The elevation of both AFP-L3 and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum AFP is significantly related to portal vein invasion or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC. Gender, Age, AFP-L3, AFP, DCP (GALAD) Score and Probability of HCC: Biomarkers of HCC include AFP, AFP-L3, and DCP. The GALAD model combines these three biomarkers with the patient's gender and age to estimate the probability of HCC in patients with chronic liver disease based on the following equation Z = -10.08 + 0.09 x age + 1.67 x sex + 2.34 log(10) (AFP) + 0.04 x AFP - L3 + 1.33 x log(10) (DCP), where sex = 1 for males, 0 for females. The probability estimate of HCC is calculated as follow Pr(HCC) = exp(Z)/(1 + exp[Z]). The GALAD model has been demonstrated to have higher diagnostic accuracy for the detection of HCC when compared to the use AFP, AFP-L3, and DCP markers alone or in combination. The performance of the GALAD score has also been reported to be superior to ultrasound for HCC detection.

Useful For: Risk assessment for development of hepatocellular carcinoma in patients with chronic hepatitis B/C.
liver disease

**Interpretation:** Alpha-fetoprotein (AFP)-L3 results of 10% or more are associated with a 7-fold increased risk of developing hepatocellular carcinoma (HCC). Patients with AFP-L3 levels of 10% or more should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. Total serum AFP results above 200 ng/mL are highly suggestive of a diagnosis of HCC. In patients with liver disease, a total serum AFP level above 200 ng/mL is near 100% predictive of HCC. With decreasing total AFP levels, there is an increased likelihood that chronic liver disease, rather than HCC, is responsible for the AFP elevation. Based on a retrospective study at Mayo Clinic, for patients with total AFP levels 200 ng/mL or less, AFP-L3 specificity approaches 100% for HCC when its percentage exceeds 35% of the total AFP. (4) AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life.

Des-gamma-carboxy prothrombin (DCP): In patients with an elevated DCP result (> or =7.5 ng/mL), the risk of developing HCC is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%). Gender, Age, AFP-L3, AFP, DCP (GALAD) Score and Probability of HCC: The probability of the presence of HCC is estimated from the GALAD model score. Higher GALAD model scores correlate with increased risk of HCC. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve of the GALAD score was 0.95 for all HCC detection, and 0.92 for the detection of early stage HCC. Additionally, the AUC of the GALAD score (0.95) was higher than that of ultrasound alone for all HCC detection (AUC of 0.82, P <0.01). The sensitivity and specificity performance characteristics of the GALAD score for HCC will be influenced by the selected GALAD score cut-off. For example at an optimal AUC cutoff of -0.76, the GALAD score had 91% sensitivity and 85% specificity for HCC detection. At a more specific GALAD score cutoff of 0.88, the observed sensitivity was 80% for HCC detection with an observed specificity of 97%. The GALAD model was developed and validated in patient cohorts with a prevalence of HCC ranging from 35% to 49%. The performance of the model may be altered in populations with different HCC prevalence. In addition, the clinical performance of the GALAD score varies by etiology of HCC and therefore may be different in different regions of the world.

**Reference Values:**

**TOTAL ALPHA-FETOPROTEIN (AFP):**

<4.7 ng/mL

**AFP L3-PERCENT:**

<10%

**DES-GAMMA-CARBOXY PROTHROMBIN:**

<7.5 ng/mL

**GAL1:**

Not applicable

**GAL2:**

Not applicable

**Clinical References:**

HEPAT
70456
**Hepatocyte Immunostain, Technical Component Only**

**Clinical Information:** Normal liver tissue is positive with a distinct granular cytoplasmic staining of hepatocytes. Bile ducts and nonparenchymal liver cells are negative.

**Useful For:** Distinguishing hepatocellular carcinoma from other types of cancer

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

HNF1B
70461
**Hepatocyte Nuclear Factor 1Beta Immunostain, Technical Component Only**

**Clinical Information:** Hepatocyte nuclear factor-1beta (HNF-1beta) is a transcription factor that regulates the transcription of the TCF2 gene into proteins. HNF-1beta has been shown to be upregulated in ovarian clear cell carcinoma.

**Useful For:** Diagnosis of ovarian clear cell carcinoma and endometrial clear cell carcinoma

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Fadare O, Zhao C, Khabele D, et al: Comparative analysis of napsin A, alpha-methylacyl-coenzyme A racemase (AMACR, P504S), and hepatocyte nuclear factor 1 beta as diagnostic markers of ovarian clear cell carcinoma: an immunohistochemical study of 279 ovarian
**Hepatosplenomegaly Panel, Blood**

**Clinical Information:** Hepatosplenomegaly is a presenting or accompanying feature for many different inborn errors of metabolism. It typically is a consequence of chronic hepatic dysfunction or abnormal storage of lipids, sugars, or other improperly metabolized analytes due to a particular enzymatic deficiency. The diagnosis can occasionally be narrowed down by consideration of clinical symptoms; however, clinical diagnosis can be difficult due to similarity of clinical features across disorders as well as phenotypic variability. Therefore, screening tests can play an important role in the workup of a patient presenting with hepatosplenomegaly who may have a lysosomal or lipid storage disorder. The conditions detected in this assay are cerebrotendinous xanthomatosis, Gaucher disease, and Niemann-Pick disease types A, B, and with a lower sensitivity and specificity C. Patients with abnormal results should have follow-up enzymatic or molecular testing for confirmation of diagnosis. Conditions Identified By Method Disorder Onset Analyte detected Gene Incidence Cerebrotendinous xanthomatosis (CTX) Infancy - adulthood 7-Alpha-hydroxy-4-cholesten-3-one (7aC4) 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (12aC4) CYP27A1 1 in 50,000 As high as 1 in 400 in Druze population. Phenotype: early onset diarrhea, cataracts, tendon/cerebral xanthomas, osteoporosis, neuropsychological manifestations, liver disease/hepatosplenomegaly. Gaucher disease Type I: childhood/adult Types II/III: neonatal-early childhood Glucopsychosine (GPSY) GBA Type I: 1 in 30,000 to 1 in 100,000 Types II/III: 1 in 100,000 Phenotype: all types exhibit hepatosplenomegaly and hematological abnormalities. Type I: organomegaly, thrombocytopenia, and bone pain. Absence of neurologic symptoms. Types II/III: primary neurologic disease, developmental delay/regression, hepatosplenomegaly, lung disease. Patients with type II typically die by age 2-4.Â Patients with type 3 may have a less progressive phenotype and may survive into adulthood.Â Niemann-Pick type A/B (NPA, NPB) NPA: neonatal NPB: birth-adulthood Lyso-sphingomyelin (LSM) lyso-sphingomyelin 509 (LSM 509) SMPD1 Combined incidence 1 in 250,000 Phenotype: NPA: feeding difficulties, jaundice, hepatosplenomegaly, neurologic deterioration, lung disease, hearing and vision impairment, cherry red macula, death usually by age 3. NPB: mainly limited to visceral symptoms; hepatosplenomegaly, stable liver dysfunction, pulmonary compromise, osteopenia. Niemann-Pick type C (NPC) Variable (perinatal-adulthood) Cholestane-3 beta, 5 alpha, 6 beta-triol (COT) lyso-sphingomyelin 509 (LSM 509) NPC1 or NPC2 1 in 120,000 to 1 in 150,000 Phenotype: Variable clinical presentation. Ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, seizures, +/-hepatosplenomegaly. Patients with Fabry disease may also be identified by this assay. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. Normal values of LGb3 do not rule out Fabry disease. Patients with Fabry disease do not have hepatosplenomegaly as an accompanying feature.

**Useful For:** As a component of the initial evaluation of a patient presenting with hepatosplenomegaly This test is not suitable for the identification of carriers.

**Interpretation:** An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7aC4) and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (12aC4) is strongly suggestive of cerebrotendinous xanthomatosis (CTX). An elevation of lyso-sphingomyelin (LSM) and lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease. An elevation of cholestane-3 beta, 5 alpha, 6 beta-triol (COT) lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick disease type C (NPC). An elevation of glucopsychosine is indicative of Gaucher disease.

**Reference Values:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLESTANE-3-BETA,5-ALPHA,6-BETA-TRIOL</td>
<td>&lt; or =0.800 nmol/mL</td>
</tr>
<tr>
<td>LYSO-SPHINGOMYELIN</td>
<td>&lt; or =0.100 nmol/mL</td>
</tr>
</tbody>
</table>
supranuclear gaze palsy, dystonia, progressive speech deterioration, seizures, +/- hepatosplenomegaly. Patients with Fabry disease may also be identified by this assay. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. Normal values of LGb3 do not rule-out Fabry disease. Patients with Fabry disease do not have hepatosplenomegaly as an accompanying feature.

**Useful For:** As a component of the initial evaluation of a patient presenting with hepatosplenomegaly using dried blood spot specimens This test is not suitable for the identification of carriers. This test should not be used as a monitoring tool for patients with confirmed diagnoses.

**Interpretation:** An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7a-C4) and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4) is strongly suggestive of cerebrotendinous xanthomatosis (CTX). An elevation of lyso-sphingomyelin (LSM) and lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease. An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol (COT) lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick disease type C (NPC). An elevation of glucosyphosphosine is indicative of Gaucher disease.

**Reference Values:**

<table>
<thead>
<tr>
<th><strong>Chemical Analysis</strong></th>
<th><strong>Cutoff</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLESTANE-3-BETA, 5-ALPHA, 6-BETA-TRIOL</td>
<td>&lt; or = 0.800 nmol/mL</td>
</tr>
<tr>
<td>LYSO-SPHINGOMYELIN</td>
<td>&lt; or = 0.100 nmol/mL</td>
</tr>
<tr>
<td>GLUCOSYPSCHOSINE</td>
<td>&lt; or = 0.040 nmol/mL</td>
</tr>
<tr>
<td>7-ALPHA-HYDROXY-4-CHOLESTEN-3-ONE (7a-C4)</td>
<td>&lt; or = 0.750 nmol/mL</td>
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<tr>
<td>7-ALPHA,12-ALPHA-DIHYDROXYCHOLEST-4-en-3-ONE (7a12aC4)</td>
<td>&lt; or = 0.250 nmol/mL</td>
</tr>
<tr>
<td>GLOBOTRIAOSYLSPHINGOSINE</td>
<td>&lt; or = 0.034 nmol/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**

disorders as well as phenotypic variability. Therefore, screening tests can play an important role in the workup of a patient presenting with hepatosplenomegaly who may have a lysosomal or lipid storage disorder. The conditions detected in this assay are cerebrotendinous xanthomatosis, Gaucher disease, and Niemann-Pick disease types A, B, and C. Patients with abnormal results should have follow-up enzymatic or molecular testing for confirmation of diagnosis. Conditions Identifiable By Method

**Disorder Onset Analyte detected Gene Incidence**

**Cerebrotendinous xanthomatosis (CTX)**

- **Infancy-adulthood**
- **7-Alpha-hydroxy-4-cholesten-3-one (7a-C4)**
- **7-alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4)**

**CYP27A1**

- **1 in 50,000**
- **As high as 1 in 400 in Druze population.**

**Phenotype:** early onset diarrhea, cataracts, tendon/cerebral xanthomas, osteoporosis, neuropsychological manifestations, liver disease/hepatosplenomegaly. Gaucher disease Type I:

- **childhood/adult Types II/III:** neonatal-early childhood
- **Glucopsychosine (GPSY) GBA**

- **Type I:** 1 in 30,000 to 1 in 100,000
- **Types II/III:** 1 in 100,000

**Phenotype:** all types exhibit hepatosplenomegaly and hematological abnormalities. Type I: organomegaly, thrombocytopenia, and bone pain. Absence of neurologic symptoms. Types II/III: primary neurologic disease, developmental delay/regression, hepatosplenomegaly, lung disease. Patients with Type II typically die by age 2 to 4. Patients with Type 3 may have a less progressive phenotype and may survive into adulthood. Niemann-Pick type A/B (NPA/NPB) NPA: neonatal NPB: birth-adulthood

- **Lyso-sphingomyelin (LSM) SMPD1**

- **Combined incidence 1 in 250,000**

**Phenotype:** NPA: feeding difficulties, jaundice, hepatosplenomegaly, stable liver dysfunction, pulmonary compromise, osteopenia. Niemann-Pick type C (NPC) Variable (perinatal-adulthood)

- **Cholestane-3 beta, 5-alpha, 6-beta-triol (COT) lyso-sphingomyelin 509 (LSM 509) NPC1 or NPC2**

- **1 in 120,000 to 1 in 150,000**

**Phenotype:** Variable clinical presentation. Ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, seizures, +/- hepatosplenomegaly. Patients with testing indicative of one of the above disorders should have follow-up enzymatic or molecular testing for confirmation of diagnosis.

**Useful For:** As a component to the initial evaluation of a patient presenting with hepatosplenomegaly using plasma specimens This test is not suitable for the identification of carriers. This test should not be used as a monitoring tool for patients with confirmed diagnoses.

**Interpretation:** An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7a-C4) and 7-alpha,12-alpha-dihydroxycholesterol-4-en-3-one (7a12aC4) is strongly suggestive of cerebrotendinous xanthomatosis (CTX). An elevation of glucopsychosine (GPSY) is indicative of Gaucher disease. An elevation of lyso-sphingomyelin (LSM) and lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease. An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol (COT) lyso-sphingomyelin 509 (LSM 509) is highly suggestive of Niemann-Pick disease type C (NPC).

**Reference Values:**

**CHOLESTANE-3-BETA, 5-ALPHA, 6-BETA-TRIOL**

Cutoff: ≤ 0.070 nmol/mL

**7-KETOCHESTEROL**

Cutoff: ≤ 0.100 nmol/mL

**LYSO-SPHINGOMYELIN**

Cutoff: ≤ 0.100 nmol/mL

**GLUCOPSYCHOSINE**

Cutoff: ≤ 0.003 nmol/mL

**7-ALPHA-HYDROXY-4-CHOLESTEN-3-ONE (7a-C4)**

Cutoff: ≤ 0.300 nmol/mL

**7-ALPHA,12-ALPHA-DIHYDROXYCHOLEST-4-en-3-ONE (7a12aC4)**

Cutoff: ≤ 0.100 nmol/mL

**HER-2/neu, Quantitative, ELISA**

**Reference Values:**
Reference Range: 0.0 - 15.0 ng/mL

Note: Graph attached as a supplemental report in MayoAccess

**Test Performed By:** LabCorp Burlington
1447 York Court
Burlington, NC 27215-2230

**Clinical References:**

**HER2 Amplification Associated with Breast Cancer, FISH, Tissue**

**Clinical Information:** HER2 (ERBB2: c-erb-b2) is an oncogene on the long arm of chromosome 17 that is amplified in approximately 15% to 20% of breast cancers. Amplification or overexpression of HER2 has been shown to be associated with shorter disease-free survival and poorer overall survival in breast cancers. Patients with HER2 gene amplification or overexpression are candidates for treatment with the drugs that target the human epidermal growth factor receptor 2 (HER2) protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab). FISH with labeled DNA probes to the pericentromeric region of chromosome 17 and to the HER2 locus can be used to determine if a patient's breast cancer has HER2 gene amplification. Immunohistochemical analysis is used to determine if a tumor exhibits HER2 overexpression.

**Useful For:** A predictive marker for patients with both node-positive or node-negative primary and metastatic breast cancer. Patients with HER2 amplification that may be candidates for therapies targeting the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 overexpression by immunohistochemistry, and for certain histologic subtypes with aberrant patterns of HER2 expression seen by immunohistochemistry (eg, micropapillary carcinoma)

**Interpretation:** An interpretive report will be provided. Results are interpreted utilizing the current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines. Under the 2018 Focused Update to the ASCO/CAP Guidelines, reflex immunohistochemistry (IHC) is performed for certain categories of results, known as Groups 2, 3, and 4. These categories are shown in the table below (Group 4 is the category formerly referred to as FISH "equivocal"). If reflex IHC is performed and is either negative (0, 1+) or positive (3+), the result of the
FISH assay is considered resolved by IHC as either negative or positive. If the IHC assay shows an equivocal (2+) result, then the FISH slide is re-scored within the areas showing the most intense membranous (2+) staining and the final FISH result is used to determine whether the result is negative or positive. ASCO/CAP Result Category HER2:D17Z1 ratio; average HER2 copies per cell Reporting approach per 2018 ASCO/CAP guidelines Group 1 HER2:D17Z1=2.00; HER2/cell > or <4.0 Positive Group 2 HER2:D17Z1=2.00; HER2/cell <4.0 Reflex IHC; FISH re-analysis if 2+ Group 3 HER2:D17Z1<2.00; HER2/cell > or <6.0 Reflex IHC; FISH re-analysis if 2+ Group 4 HER2:D17Z1<2.00; HER2/cell > or =4.0 <6.0 Reflex IHC; FISH re-analysis if 2+ Group 5 HER2:D17Z1<2.00; HER2/cell <4.0 Negative The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values:
An interpretive report will be provided.

Clinical References:

HER2 Amplification Associated with Gastroesophageal Cancer, FISH, Tissue

Clinical Information: Gastroesophageal cancer is one of the most commonly diagnosed cancers. To date, chemotherapy for gastroesophageal cancer is often ineffective and its prognosis remains poor. Recent studies suggest that the HER2 oncogene can be used as a marker to identify aggressive disease. In much the same way as was demonstrated for HER2-positive breast cancer, the HER2 gene status in gastroesophageal cancers can be used to determine treatment approaches. Amplification of the HER2 gene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers. Patients whose tumors demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab).
Useful For: Guiding therapy for patients with primary or metastatic gastroesophageal tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab) Confirming the presence or absence of HER2 amplification in cases with 2+ (equivocal) HER2 overexpression by immunohistochemistry

Interpretation: An interpretive report will be provided. Results are interpreted utilizing the 2016 College of American Pathologists (CAP)/American Society for Clinical Pathology (ASCP)/American Society of Clinical Oncology (ASCO) guidelines for gastric tumors, and the guidelines used by the Trastuzumab for Gastric Cancer (ToGA) trial. Specimens with equivocal results as defined by 2016 CAP/ASCP/ASCO guidelines will not have reflex testing performed using an alternative FISH probe set. The report will include a complete interpretation including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis or response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values: An interpretative report will be provided.


H2UR 65882

HER2 Amplification Associated with Urothelial Carcinoma, FISH, Tissue

Clinical Information: Human epidermal growth factor receptor 2 (HER2) plays a fundamental role in cell growth, survival, and migration. The assessment of HER2 gene status is crucial for the management of breast cancer. Studies have shown that HER2 is also expressed in a proportion of urothelial carcinoma of the urinary bladder (UCB), making it a potential target for UCB therapy. HER2-positive gene status is associated with aggressive UCB and provides independent prognostic information. Assessment of HER2 status may be used to identify patients at high risk of disease progression.

Useful For: Guiding therapy for patients with primary or metastatic urothelial tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry, and for certain histologic subtypes with aberrant patterns of HER2 expression.
seen by immunohistochemistry (eg, micropapillary carcinoma).

**Interpretation:** An interpretive report will be provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors. Specimens with equivocal (Group 4) results as defined by 2013 ASCO/CAP guidelines will no longer have reflex testing performed using an alternative FISH probe set. The report will include a complete interpretation including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**HER2 Amplification, Miscellaneous Tumor, FISH, Tissue**

**Clinical Information:** Amplification of the HER2 oncogene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival and poorer overall survival in some cancers. Patients whose breast or gastroesophageal cancers demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab, lapatinib).

**Useful For:** Guiding cancer therapy, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry

**Interpretation:** An interpretive report will be provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors. Specimens with equivocal (Group 4) results as defined by 2013 ASCO/CAP guidelines will not have reflex testing performed using an alternative FISH probe set. The report will include a complete interpretation including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit a high level of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have a similar prognosis or response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and may be candidates for treatments that target the HER2 protein or its downstream pathways.
Reference Values:
An interpretative report will be provided.


HER2 Immunostain, Technical Component Only

**Clinical Information:** The human HER2 gene (also known as ERBB2 or NEU) encodes a protein often referred to as HER2 protein or P185(HER2). The HER2 protein is a membrane receptor tyrosine kinase with homology to the epidermal growth factor receptor (EGFR or HER1). The HER2 protein is a normal component expressed by a variety of epithelial cell types.

**Useful For:** Identification of HER2 protein overexpression in formalin-fixed, paraffin-embedded tissue sections

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


HER2, Breast, DCIS, Quantitative Immunohistochemistry, Manual No Reflex

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

**Useful For:** Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections in ductal carcinoma in situ or solid/intracystic papillary carcinoma breast tissue This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer

**Interpretation:** Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Reference Values:** Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Clinical References:** 1. Riber-Hansen R, Vainer B, Steiniche T: Digital image analysis: a review of reproducibility, stability and basic requirements for optimal results. Apmis 2012

**HER2, Breast, DCIS, Quantitative Immunohistochemistry, Manual with HER2 FISH Reflex**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

**Useful For:** Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections in ductal carcinoma in situ or solid/intracycstic papillary carcinoma breast tissue with a reflex to FISH testing if the specimen is equivocal (2+)

**Interpretation:** Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Reference Values:** Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.


**HER2, Breast, Quantitative Immunohistochemistry, Automated with HER2 FISH Reflex**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer. This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer.

**Useful For:** Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections using automated quantitative immunohistochemistry

**Interpretation:** Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

**Reference Values:** Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation
guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.


**HERBN**

**HER2, Breast, Quantitative Immunohistochemistry, Automated, No Reflex**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

**Useful For:** Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections without a reflex to FISH testing This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer

**Interpretation:** Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

**Reference Values:** Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.


**HERGM**

**HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

**Useful For:** Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections (with reflex to FISH testing)

**Interpretation:** Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or negative (0 or 1+). Equivocal (2+) cases will automatically reflex to FISH testing at an additional
HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual, No Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

Useful For: Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections (no reflex to FISH testing)

Interpretation: Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or negative (0 or 1+)

Reference Values: Reported as negative (0, 1+), equivocal (2+), and positive (3+)


Hereditary Colon Cancer CGH Array

Reference Values: Only orderable as a reflex. For further information see:
AXINZ / AXIN2 Gene, Full Gene Analysis
BMPRZ / BMPR1A Gene, Full Gene Analysis
MLH3Z / MLH3 Gene, Full Gene Analysis
PTENZ / PTEN Gene, Full Gene Analysis
SMADZ / SMAD4 Gene, Full Gene Analysis
STKZ / STK11 Gene, Full Gene Analysis
TP53Z / TP53 Gene, Full Gene Analysis
CDH1Z / CDH1 Gene, Full Gene Analysis
M1M2Z / MLH1/MSH2 Genes, Full Gene Analysis
MLH1Z / MLH1 Gene, Full Gene Analysis
MSH2Z / MSH2 Gene, Full Gene Analysis
MSH6Z / MSH6 Gene, Full Gene Analysis
APCZ / APC Gene, Full Gene Analysis

For information regarding hereditary colon cancer, see FMTT / Familial Mutation, Targeted Testing.
**Hereditary Colon Cancer Multi-Gene Panel, Varies**

**Clinical Information:** Colorectal cancer occurs in approximately 5% to 6% of individuals in the general population. In rare cases, individuals with a family history of colorectal cancer may be at increased risk for colon and other cancers due to a single-gene predisposition syndrome, known as hereditary colorectal cancer. The 2 most common hereditary colorectal cancer syndromes are Lynch syndrome and familial adenomatous polyposis (FAP). However, there are multiple other genes that are also known to cause to hereditary colorectal cancer or contribute to an increased risk for colorectal cancer. This panel uses next-generation sequencing (NGS), array comparative genomic hybridization (aCGH), and other technologies to evaluate for germline variants in 17 genes known to be associated with an increased risk for colon cancer development. Two of the genes listed, CHEK2 and MLH3, are not associated with a known hereditary cancer syndrome defined by a distinct spectrum of tumors. However, literature suggests that variants in these genes may confer an increased risk for colon cancer and, therefore, are predicted to contribute to cancer risk in patients and families. Gene Known association MLH1 Lynch syndrome MSH2 Lynch syndrome MSH6 Lynch syndrome PMS2 Lynch syndrome EPCAM Lynch syndrome APC Familial adenomatous polyposis MYH/MutYH MYH-associated polyposis SCG5/GREM1 Hereditary mixed polyposis syndrome STK11 Peutz-Jeghers syndrome SMAD4 Juvenile polyposis syndrome BMP1A Juvenile polyposis syndrome PTEN PTEN hamartoma tumor syndrome (ie, Cowden syndrome) CDH1 Hereditary diffuse gastric cancer AXIN2 Oligodontia-colorectal cancer syndrome TP53 Li-Fraumeni syndrome CHEK2 Low-risk gene MLH3 Low-risk gene Indications for testing include but are not limited to: -Patients in whom no specific colorectal cancer syndrome is evident but for whom there is a clear familial component -Patients whose family history is consistent with familial colorectal cancer type X(1) -Patients with a strong suspicion for a single-gene hereditary colon cancer syndrome based on an autosomal dominant pattern of colon cancer in the family -Patients with a personal or family history of colonic polyposis

**Useful For:** Providing a comprehensive evaluation for hereditary colon cancer in patients with a personal or family history suggestive of a hereditary colon cancer syndrome Serving as a second-tier test for patients in whom previous targeted gene variant analyses for specific hereditary colorectal cancer-related genes were negative Establishing a diagnosis of a hereditary colon cancer syndrome in some cases, allowing for targeted cancer surveillance of associated extra-colonic organs known to be at increased risk for cancer Identifying variants within genes known to be associated with increased risk for colon cancer allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

Hereditary Erythrocytosis Mutations, Whole Blood

Clinical Information: Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase; BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal level Normal BPDM Recessive Normal level Decreased Beta globin Dominant Normal level to increased Decreased Alpha globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isof orm is PHD2, which is encoded by the PHD2 (EGLN1) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels and normal p50 values (see Table).

Useful For: Definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC count, hemoglobin, or hematocrit This test is not intended for prenatal diagnosis.

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

Reference Values: An interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A: The complete evaluation of erythrocytosis:
Hereditary Hemolytic Anemia Comprehensive Panel, Next-Generation Sequencing, Varies

**Clinical Information:** Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This test is best interpreted in the context of protein studies and peripheral blood findings. This can be provided by ordering the HAEVP / Hemolytic Anemia Evaluation Profile test. Please fill out the information sheet and indicate that NGS testing was also ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results. Hereditary hemolytic anemias are caused by defects in one or more of the genes that control RBC production, metabolism, or structure, resulting in faulty erythropoiesis, cell membranes, or enzymes required for normal RBC function. This panel aids in the diagnosis and treatment for hereditary (congenital) hemolytic anemia. The panel includes genes known to cause hereditary anemia including those implicated in RBC enzyme, RBC membrane/RBC hydration, and congenital dyserythropoietic anemia disorders. This panel can aid in the differential diagnosis of early onset and lifelong myopathic or neurologic syndromes, especially if associated with hemolysis. Specifically, this panel assays genes associated with hereditary spherocytosis (HS), hereditary elliptocytosis (HE), hereditary pyropoikilocytosis (HPP), Southeast Asian ovalocytosis, hereditary stomatocytosis (both overhydrated and dehydrated/hereditary xerocytosis subtypes), and cryohydrocytosis. Hereditary stomatocytosis is a RBC membrane permeability disorder that can manifest as the more common dehydrated hereditary stomatocytosis (DHS), also known as hereditary xerocytosis (HX) and the rarer overhydrated hereditary stomatocytosis (OHST) subtypes. These disorders are important to confirm or exclude as splenectomy has been associated with an increased risk for serious venous thrombosis and thromboembolism events and is contraindicated in published guidelines. It also includes genes associated with RBC enzymopathies, ranging from the common glucose 6 phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) deficiencies, to the rarer disorders of adenylate kinase (AK1), hexokinase (HK1), phosphofructokinase (PFKM), phosphoglycerate kinase (PGK1), pyruvate kinase (PKLR), glutathione pathway, and triosephosphate isomerase (TP1). This panel also includes multiple genes associated with congenital dyserythropoietic anemia (CDA), types 1a, 1b, 2, 3, and 4. CDA is a disorder of ineffective erythropoiesis associated with distinctive bone marrow morphologic changes. A limited number of the most common genes associated with Fanconi anemia (FA) and Diamond-Blackfan anemia (DBA) are also analyzed by this panel; however, this panel is not intended as a thorough investigation of FA or DBA.

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemolytic anemias, including RBC membrane/hydration disorders, RBC enzymopathies and congenital dyserythropoietic anemia Comprehensive testing for patients in whom previous targeted gene mutation analyses were negative for a specific hereditary hemolytic anemia.
anemia. Establishing a diagnosis of a hereditary hemolytic anemia or related disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration (2) Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(6,7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HHTGP**
**Hereditary Hemorrhagic Telangiectasia Gene Panel, Varies**

**Clinical Information:** Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVM, or telangiectasias, develop predominantly on the face, oral cavity, and hands, and spontaneous, recurrent epistaxis (nose bleeding) is a common presenting sign. Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of larger AVM, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively. HHT is inherited in an autosomal dominant manner and occurs with wide ethnic and geographic distribution. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, increasing to 80% to 90% by age 21 years, and as many as 90% to 95% of affected individuals eventually developing recurrent epistaxis. HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing allows for the confirmation of a suspected genetic disease. Confirmation of a diagnosis allows for proper treatment and management of the disease, preconception or prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening. Two genes are most commonly associated with HHT: the endoglin gene (ENG), and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1). ENG and
ACVRL1 encode membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Variants in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVM, whereas ACVRL1 variants occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVM. The majority of variants in ENG and ACVRL1 are missense, nonsense, splice site, or small intragenic deletions and insertions. Approximately 10% of ENG and ACVRL1 variants are large genomic deletions and duplications (also known as dosage alterations). Approximately 60% to 80% of patients with HHT will have a variant detected in ENG or ACVRL1. Pathogenic variants in the SMAD4 gene are the third most common identifiable cause of HHT, accounting for approximately 10% of HHT patients who test negative for ENG and ACVRL1, and approximately 1% to 2% of total HHT cases. Pathogenic SMAD4 variants cause autosomal dominant juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPH7), which includes features of juvenile polyposis syndrome (JPS) and HHT. JPS is characterized by hamartomatous polyps of the gastrointestinal tract and increased risk of gastrointestinal cancer. SMAD4 variants have also been detected in families presenting with JPS or HHT only. Pathogenic variants in the GDF2 gene (also known as BMP9) are a rare cause of HHT. In a study of 191 individuals with clinically suspected HHT and no variants in ENG, ACVRL1, or SMAD4, 3 unrelated individuals were found to carry a rare missense variant in GDF2. Pathogenic variants in the RASA1 gene cause capillary malformation-arteriovenous malformation syndrome (CMAVM). CMAVM is characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly localized to the face and limbs. Patients may also have arteriovenous malformations (AVM) and arteriovenous fistulas (AVF). In some cases, pathogenic RASA1 variants may be found in individuals clinically suspected to have HHT. Individuals with a pathogenic RASA1 variant may have a clinical diagnosis of Parkes Weber syndrome (PWS), with multiple micro-AVF associated with a cutaneous capillary stain and excessive soft tissue and skeletal growth of an affected limb.

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Protein</th>
<th>OMIM</th>
<th>Inheritance</th>
<th>Phenotype/Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACVRL1</td>
<td>Activin A receptor like type 1</td>
<td>601284</td>
<td>AD</td>
<td>Telangiectasia, hereditary hemorrhagic, type 2</td>
</tr>
<tr>
<td>ENG</td>
<td>Endoglin</td>
<td>131195</td>
<td>AD</td>
<td>Telangiectasia, hereditary hemorrhagic, type 1</td>
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<td>GDF2</td>
<td>Growth differentiation factor 2</td>
<td>605120</td>
<td>AD</td>
<td>Telangiectasia, hereditary hemorrhagic, type 5</td>
</tr>
<tr>
<td>RASA1</td>
<td>RAS p21 protein activator 1</td>
<td>139150</td>
<td>AD</td>
<td>Capillary malformation-arteriovenous malformation, Parkes Weber syndrome</td>
</tr>
<tr>
<td>SMAD4</td>
<td>SMAD family member 4</td>
<td>600993</td>
<td>AD</td>
<td>Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Myhre syndrome</td>
</tr>
</tbody>
</table>

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT) or a related disorder. Second-tier testing for patients in whom previous targeted gene variant analyses for specific HHT genes were negative. Establishing a diagnosis of HHT and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved identifying variants within genes known to be associated with HHT and allowing for predictive testing of at-risk family members.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


HPPAN 35640

Hereditary Pancreatitis Panel, Varies

Clinical Information: Hereditary pancreatitis (HP) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations. Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. PRSS1: The most common monogenic cause of HP is the presence of a mutation in the cationic trypsinogen (PRSS1) gene. Mutations in the PRSS1 gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced or tropical pancreatitis. Although several mutations have been identified, the R122H, N29I, and A16V mutations are the most common disease-causing mutations in PRSS1 associated with HP. Data suggests that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%. SPINK1: Biallelic mutations in the SPINK1 gene have been associated with increased susceptibility to chronic pancreatitis especially in families without PRSS1 mutations; however, it is unknown if biallelic mutations alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous SPINK1 mutations appear to modify disease severity when observed in combination with mutations in other genes. Unlike PRSS1 mutations, SPINK1 mutations have been associated with alcohol-induced and tropical pancreatitis. CFTR: Pancreatitis is a known manifestation of an atypical CFTR-related disorder in which 2 mutations in the CFTR gene are identified. However, CFTR mutations can also co-occur with mutations in CTRC, SPINK1, or CASR to confer pancreatitis disease susceptibility. When observed in the context of a SPINK1 mutation, for example, heterozygous mutations in CFTR are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population. CTRC: Mutations in CTRC have been observed in individuals with chronic pancreatitis in association with other risk factors such as mutations in CFTR or SPINK1 or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of CTRC mutations in the context of other risk factors as opposed to CTRC mutations alone.

Useful For: Confirmation of suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis Identification of gene mutations contributing to pancreatitis in an individual or family Identification of gene mutations to allow for predictive and diagnostic testing in family members

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

Reference Values:
An interpretive report will be provided.

HSAN1
604922

Hereditary Sensory and Autonomic Neuropathy, Type I, Serum

Clinical Information: Sphingolipids, a class of lipids derived from sphingosine, are essential components of plasma membranes and lipoproteins. They are synthesized from L-serine and palmitoyl-CoA by the enzyme serine palmitoyltransferase. Deoxysphingolipids (dSLs) are atypical sphingolipids derived from the amino acids alanine or glycine instead of L-serine and cannot be degraded by normal catabolic pathways. Pathologically elevated dSLs have been identified as potential biomarkers in a variety of conditions such as hereditary sensory and autonomic neuropathy type 1 (HSAN1), type 2 diabetes mellitus, metabolic syndrome, mitochondrial disease, glycogen storage disease type 1, and possibly disorders of serine biosynthesis. Hereditary sensory and autonomic neuropathies are a group of clinically and genetically heterogeneous peripheral neuropathies. HSAN1 is inherited in an autosomal dominant fashion and is typically characterized by a later onset loss of pain and temperature sensation in the hands and feet, which can be accompanied by shooting pain attacks, lancinating pain, and skin ulcers predominantly affecting the lower limbs. While variants in 5 different genes (SPTLC1, SPTLC2, ATL1, RAB7A and DNMT1) have been linked to HSAN1, the majority of variants are in SPTLC1 and SPTLC2, which encode two of three subunits of the serine palmitoyltransferase (SPT) enzyme. Variants in these two genes lead to a shift in SPT substrate specificity from L-serine to L-alanine, which ultimately produces two neurotoxic deoxysphingolipids, 1-deoxymethylsphinganine and 1-deoxysphinganine. The accumulation of these metabolites in the cells and serum of affected patients is thought to cause the clinical features associated with HSAN1. A recent clinical trial found that L-serine supplementation safely reduced levels of 1-deoxysphingolipids in humans and suggested that supplementation may offer a clinical benefit.(1)

Useful For: Diagnosis of patients with clinical features suggestive of hereditary sensory and autonomic neuropathy, type I caused by variants in SPTLC1 and SPTLC2 Monitoring of patients with hereditary sensory and autonomic neuropathy, type I caused by variants in SPTLC1 and SPTLC2

Interpretation: Elevation of deoxysphingolipids may indicate hereditary sensory and autonomic neuropathy, type I caused by variants in SPTLC1 and SPTLC2. Deoxysphingolipids may also be elevated in patients with other conditions such as type 2 diabetes mellitus, metabolic syndrome, mitochondrial disorders, glycogen storage disease type 1, and possibly disorders of serine biosynthesis.

Reference Values:
- Sphinganine: < or =18.0 ng/mL
- 1-deoxysphinganine: < or =0.25 ng/mL
- 1-deoxymethylsphinganine: < or =0.04 ng/mL
- Sphingosine: < or =80.0 ng/mL
- 1-deoxysphingosine: < or =0.05 mg/mL
- 1-deoxymethylsphingosine: < or =0.09 mg/mL

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. HSV causes various clinical syndromes. Anatomic sites infected include skin, lips and oral cavity, eyes, genital tract, and central nervous system. Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before age 10. After primary infection with VZV, the virus persists in latent form and may emerge (usually in adults age 50 and older) clinically to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

Useful For: Rapid diagnosis of herpes simplex virus and varicella-zoster virus infections

Interpretation: Herpes Simplex Virus (HSV) PCR: This is a qualitative assay; results are reported either as negative, positive, or indeterminate for HSV type 1 or HSV type 2. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus. Varicella-Zoster Virus (VZV) PCR: Detection of VZV DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler PCR assay does not yield positive results with other herpesvirus gene targets (cytomegalovirus, Epstein-Barr virus).

Reference Values:

HERPES SIMPLEX VIRUS (HSV) PCR
Negative

VARICELLA-ZOSTER VIRUS PCR
Negative

Herpes Simplex Virus (HSV) Type 1- and Type 2-Specific Antibodies, IgG, Serum

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing, primarily using polymerase chain reaction (PCR) to detect viral DNA. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2 (eg, risk of reactivation). In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.

Useful For: Determining whether a patient has been previously exposed to herpes simplex virus (HSV) types 1 and 2. Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection. This test should not be used to diagnose active or recent infection.

Interpretation: This assay detects IgG-class antibodies to type-specific herpes simplex virus (HSV) glycoprotein G (gG) and may allow for the differentiation of infection caused by HSV types 1 and 2. The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure and does not necessarily indicate that HSV is the causative agent of an acute illness.

Reference Values:
Negative (reported as positive, negative, or equivocal)

Clinical References:
United States (2005-2010) is 53.9% and 15.7%, respectively. (3) HSV-1 has historically been associated with oral lesions, but increasingly it is also a cause of genital herpes. Both HSV-1 and HSV-2 can cause severe CNS disease. In particular, HSV encephalitis in neonates is considered a medical emergency. Even with antiviral medication, there is significant morbidity and mortality associated with HSV encephalitis, especially in neonates. Fetal and neonatal HSV infections can be acquired in utero or at the time of delivery. The greatest risk for transmitting HSV is when the mother experiences a primary HSV infection, but there is also increased risk of transmission during periods of reactivation. Primary infection and reactivation may not be symptomatic, but nevertheless result in viral transmission to the fetus or newborn. Diagnostic methods for HSV include routine viral culture, molecular testing by PCR, and serology. It is difficult to recover HSV from spinal fluid (CSF) specimens using viral culture, and a serologic response to HSV is not detectable immediately after infection. Detection of HSV by real-time PCR is now recognized as the most sensitive approach to diagnose HSV infection, especially CNS-associated HSV disease. However, it is still recommended to test neonates by viral culture when testing for potential congenital herpes by peripheral (eg, skin) swab, since PCR may detect low levels of HSV DNA or inactive virus in the absence of infectious viral particles. Infants younger than 4 weeks of age may have detectable HSV DNA on them that was shed by an infected mother, even in the absence of active HSV infection in the infant. On the other hand, a positive result by viral culture indicates the presence of live virus, suggesting active infection in the newborn. (4)

Useful For: An aid in the diagnosis of congenital herpes simplex virus (HSV) infection in patients younger than 35 days old through the recovery of HSV using viral culture (shell-vial)

Interpretation: Recovery of herpes simplex virus (HSV) from clinical specimens supports the diagnosis of congenital HSV infection. A negative result by shell vial assay should be interpreted in the context of the patient's clinical presentation and exposure history. Furthermore, testing by real-time PCR for this virus should be considered prior to ruling out HSV disease.

Reference Values:
No virus isolated

Clinical References:

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Blood

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 cause a variety of clinical syndromes. Anatomic sites infected include the skin, lips, oral cavity, eyes, genital tract, and central nervous system (CNS). Systemic disease may also occur, in which the virus may be detectable in the bloodstream. The detection of HSV-1 or HSV-2 from blood specimens may help support the diagnosis of disseminated disease associated with this virus.

Useful For: Aids in the rapid diagnosis of disseminated disease due to herpes simplex virus (HSV) Qualitative detection of HSV DNA

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2. In a small number of cases (eg, <1%), HSV is detected but this assay may not be able to provide a definitive subtype (HSV-1 versus HSV-2). This is due to mutations in the region of the HSV genome to which the PCR probes bind. When this result is observed, the report will go out as "Indeterminate", which means that HSV DNA was detected, but the assay was...
Herpes Simplex Virus (HSV), Molecular Detection, PCR, Spinal Fluid

Clinical Information: Herpes simplex virus (HSV)-1 and HSV-2 are members of the Alpha herpessviridae subfamily. HSV is an enveloped virus with a capsid containing viral DNA. Although HSV-1 and HSV-2 are closely related, the 2 viruses are serologically and genetically distinct. (1,2) HSV-1 and -2 are common causes of dermal and genital infections; however, in some cases, infection with HSV may result in central nervous system (CNS) disease that is considered a medical emergency. HSV infection of the CNS may result in encephalitis (more commonly associated with HSV-1) or meningitis (more commonly associated with HSV-2). Encephalitis is inflammation of the brain associated with clinical evidence of neurologic dysfunction. Of the pathogens reported to cause encephalitis, the majority are viruses. (3) In general, the most commonly identified etiologies in the United States are HSV, West Nile virus, and the enteroviruses, followed by other herpesviruses. (3) HSV causes about 5% to 10% of all encephalitis cases, and is one of the most common causes of identified sporadic encephalitis globally. (3) HSV encephalitis occurs in all ages, and during all seasons. HSV-1 encephalitis is more common in adults, and HSV-2 encephalitis is more common in neonates. (3) One study reported a neonatal herpes rate of 1 case per 3,200 live births in the United States. (4) Clinical features involved with HSV encephalitis include fever, hemicranial headache, language and behavioral abnormalities, memory impairment, and seizures. (3)

Useful For: Aids in the rapid diagnosis of herpes simplex virus (HSV)-1 and HSV-2 infections of the central nervous system

Interpretation: A positive result suggests the presence of herpes simplex virus (HSV)-1 and/or HSV-2 DNA in the cerebrospinal fluid (CSF) sample. A negative result suggests that HSV-1 and HSV-2 DNA are not present in the CSF sample. An invalid result points to the inability to determine presence or absence of HSV-1 or HSV-2 DNA in the CSF sample.

Reference Values: Negative

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Varies

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture.

Useful For: Aiding in the rapid diagnosis of herpes simplex virus (HSV) infections, including qualitative detection of HSV DNA in nonblood clinical specimens

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2, or HSV indeterminate. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:
Negative


Herpes Simplex Virus 1 and 2, Qualitative PCR, Blood

Clinical Information: Herpes simplex virus types 1 and 2 (HSV-1/2) are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV-1/2 can differ significantly in their clinical manifestations and severity. HSV-2 primarily causes urogenital infections and is found most often in adults. HSV-1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. In certain cases, the virus may disseminate and involve multiple organ systems, including the central nervous system. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction (PCR) or viral culture.

Useful For: Direct detection and differentiation of HSV-1 and HSV-2 DNA in whole blood specimens
from symptomatic patients who are suspected to have disseminated disease. Aids in diagnosis of HSV infection in symptomatic patients. This test is not intended to be used for prenatal screenings.

**Interpretation:** This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2 nucleic acid. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

**Reference Values:**

HERPES SIMPLEX VIRUS (HSV)-1
- Negative

HERPES SIMPLEX VIRUS (HSV)-2
- Negative

**Clinical References:**

**HERPES SIMPLEX VIRUS 1 and 2, Qualitative PCR, Varies**

**Clinical Information:** Herpes simplex virus types 1 and 2 (HSV-1/2) are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV-1 and -2 can differ significantly in their clinical manifestations and severity. HSV-2 primarily causes urogenital infections and is found most often in adults. HSV-1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction (PCR) or viral culture.

**Useful For:** Direct detection and differentiation of HSV-1 and HSV-2 DNA in various specimen types from symptomatic patients. Aids in diagnosis of HSV infection in symptomatic patients. This test is not intended to be used for prenatal screening.

**Interpretation:** This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2 nucleic acid. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

**Reference Values:**
- Negative

**Clinical References:**

HRPSV
Herpes Simplex Virus, I and II (HSV I and II) Immunostain, Technical Component Only

Clinical Information: Immunoperoxidase staining for herpes simplex virus (HSV) I and II produces nuclear and granular cytoplasmic staining of virus infected cells. HSV I and II are part of the herpes virus family that also includes Epstein Barr virus, herpes zoster, and cytomegalovirus. HSV are among the most common infectious agents of man and usually are transmitted through close personal contact. The manifestations of infection can be localized (oral lesions HSV I; genital lesions HSV II) or can cause life-threatening systemic infection in immunocompromised patients.

Useful For: Identification of herpes simplex virus I and II infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FHHV6
Herpes Virus 6 DNA, Qualitative Real-Time PCR
Reference Values:
Reference Range: Not Detected

FHV6D
Herpesvirus 6 (HHV-6) DNA, Quantitative Real-Time PCR
Reference Values:
<500 copies/mL

FHV7D
Herpesvirus 7 (HHV-7) DNA, Quantitative Real-Time PCR
Reference Values:
Reference Range: <500 copies/mL
**Herpesvirus 7 IgG and IgM Antibody Panel, IFA**

**Reference Values:**

Reference Range:

- IgG  <1:320
- IgM  <1:20

Human Herpesvirus 7 (HHV-7), a close relative of HHV-6, is found in >85% of the population, with transmission occurring in early childhood. Like HHV-6, HHV-7 is a cause of exanthem subitum (roseola infantum). Due to the ubiquitous nature of HHV-7 infection, >80% of individuals in the general population exhibit HHV-7 IgG titers >or=1:20; however, only 5% of these individuals exhibit titers >1:320. Thus, HHV-7 IgG titers > 1:320 are suggestive of recent HHV-7 infection. Detection of HHV-7 specific IgM is also indicative of recent infection.

**Herpesvirus 8 (HHV-8) DNA, Quantitative Real-Time PCR**

**Reference Values:**

Reference Range: <1000 copies/mL

**Herring, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to herring Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
Strongly positive Reference values apply to all ages.


**FHEXA**

**Hexagonal Phospholipid Neutralization**

**Reference Values:**
All ages: 0-11 sec

This is a qualitative assay and is therefore reported as positive for lupus anticoagulant or negative. The quantitative value is provided as an aid in diagnosis.

**HKC**

**Hexokinase Enzyme Activity, Blood**

**Clinical Information:** Hexokinase (HK) is the first enzymatic step in glycolysis, converting glucose to glucose-6-phosphate. Hexokinase deficiency (OMIM 235700) is a rare cause of chronic nonspherocytic hemolytic anemia and its inheritance is autosomal recessive. Clinically significant HK deficiency manifests in early onset anemia with variable severity ranging from mild to severe. Some patients show neurologic impairment of which the mechanism is unclear.

**Useful For:** The evaluation of individuals with Coombs-negative chronic hemolysis

**Interpretation:** Clinical correlation or genetic confirmation may be required to establish hexokinase (HK) deficiency as a cause of hemolytic anemia as the assayed activity level in confirmed cases can vary from markedly decreased to borderline normal levels due to a compensated increase in enzyme by reticulocytes. Comparison of hexokinase activity levels to other RBC enzyme activity can be very useful. Heterozygotes have moderately decreased to low normal HK levels and are expected to be clinically unaffected. Increased HK activity may be seen when reticulocytes are increased and is not supportive of a diagnosis of HK deficiency.

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

> or =12 months: 0.7-1.7 U/g Hb
Reference values have not been established for patients who are less than 12 months of age.

**Clinical References:**

**HK1**

**Hexokinase Enzyme Activity, Blood**

**Clinical Information:** Hexokinase (HK) is the first enzymatic step in glycolysis, converting glucose to glucose 6-phosphate. Hexokinase deficiency (OMIM 235700) is a rare cause of chronic nonspherocytic hemolytic anemia, and its inheritance is autosomal recessive. Clinically significant HK deficiency manifests in early onset anemia with variable severity ranging from mild to severe. Some patients show...
neurologic impairment of which the mechanism is unclear.

**Useful For:** The evaluation of individuals with Coombs-negative chronic hemolysis

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**Reference Values:**
> or = 12 months: 0.7-1.7 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

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**Hexosaminidase A and Total Hexosaminidase, Leukocytes**

**Clinical Information:** Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 variants in HEXA, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGA / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel that includes the most common genetic variants observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease is an autosomal recessive condition resulting from 2 variants in HEXB, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease...
have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing variant. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have genetic alterations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A, Serum). Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease. For additional testing options for Tay-Sachs and Sandhoff disease, see NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes (Tay-Sachs disease only) and NAGS / Hexosaminidase A and Total Hexosaminidase, Serum (Tay-Sachs and Sandhoff diseases) (not appropriate for Sandhoff detection in females who are pregnant or receiving hormonal contraception).

Useful For: Carrier detection and diagnosis of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease

Interpretation: Interpretation is provided with report. Hexosaminidase A usually composes more than 62% of the total hexosaminidase activity in leukocytes (normal =63%-75% A). In leukocytes, the percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs disease: 
-63% to 75% hexosaminidase A is normal (noncarrier) -58% to 62% hexosaminidase A is indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for prenatal diagnosis if desired) -less than 58% hexosaminidase A is a carrier (molecular testing recommended to discern disease-causing variants from pseudodeficiency alleles and to allow for prenatal diagnosis, if desired) -less than 20% hexosaminidase A is consistent with a diagnosis of Tay-Sachs disease In leukocytes, the total hexosaminidase in combination with the percent hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with Sandhoff disease: -greater than or equal to 76% hexosaminidase A is suggestive of a Sandhoff carrier, when the total hexosaminidase is depressed -Total hexosaminidase activity near zero with nearly 100% hexosaminidase A is consistent with Sandhoff disease

Reference Values:

HEXOSAMINIDASE TOTAL  
< or =15 years: > or =20 nmol/min/mg  
> or =16 years: 16.4-36.2 nmol/min/mg

HEXOSAMINIDASE PERCENT A  
< or =15 years: 20-80% of total

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 1314

NAGS

Hexosaminidase A and Total Hexosaminidase, Serum

Clinical Information: Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 variants in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease is an autosomal recessive condition resulting from 2 variants in the HEBX gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in
age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing variant. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have genetic alterations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A, Serum). Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results, and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Recommended test for carrier detection and diagnosis of Sandhoff disease Carrier detection and diagnosis of Tay-Sachs disease This test is not useful for pregnant females or those treated with hormonal contraception.

**Interpretation:** Interpretation is provided with report.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEXOSAMINIDASE TOTAL</td>
<td></td>
</tr>
<tr>
<td>&lt; or =15 years:</td>
<td>&gt; or =20 nmol/min/mL</td>
</tr>
<tr>
<td>&gt; or =16 years:</td>
<td>10.4-23.8 nmol/min/mL</td>
</tr>
<tr>
<td>HEXOSAMINIDASE PERCENT A</td>
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<tr>
<td>&lt; or =15 years:</td>
<td>20-90%</td>
</tr>
<tr>
<td>&gt; or =16 years:</td>
<td>56-80%</td>
</tr>
</tbody>
</table>

**Clinical References:**
**Clinical Information:** Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 variants in HEXA, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral giosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen, and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel that includes the most common genetic variants observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease is an autosomal recessive condition resulting from 2 variants in HEXB, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing variant. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have alterations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A, Serum). Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of...
the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease. For additional testing options for Tay-Sachs and Sandhoff disease, see NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes (Tay-Sachs disease only) and NAGS / Hexosaminidase A and Total Hexosaminidase, Serum (Tay-Sachs and Sandhoff diseases (not appropriate for Sandhoff detection in females who are pregnant or receiving hormonal contraception).

**Useful For:** Carrier detection and diagnosis of Tay-Sachs disease Recommended test for carrier detection of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease

**Interpretation:** Interpretation is provided with report. Hexosaminidase A usually composes greater than 62% of the total hexosaminidase activity in leukocytes (normal = 63%-75% A). In leukocytes, the percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs disease: -63% to 75% hexosaminidase A is normal (noncarrier) -58% to 62% hexosaminidase A is indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for prenatal diagnosis if desired) -less than 58% hexosaminidase A is a carrier (molecular testing recommended to discern disease-causing variants from pseudodeficiency alleles and to allow for prenatal diagnosis if desired) -less than 20% hexosaminidase A is consistent with a diagnosis of Tay-Sachs disease. In leukocytes, the total hexosaminidase in combination with the percent hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with Sandhoff disease: -greater than or equal to 76% hexosaminidase A is suggestive of a Sandhoff carrier, when the total hexosaminidase is depressed -Total hexosaminidase activity near zero with nearly 100% hexosaminidase A is consistent with Sandhoff disease

**Reference Values:**

<table>
<thead>
<tr>
<th>HEXOSAMINIDASE TOTAL</th>
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<tbody>
<tr>
<td>&lt; or =15 years: &gt; or =20 nmol/min/mg</td>
</tr>
<tr>
<td>&gt; or =16 years: 16.4-36.2 nmol/min/mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HEXOSAMINIDASE PERCENT A</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =15 years: 20-80% of total</td>
</tr>
<tr>
<td>&gt; or =16 years: 63-75% of total</td>
</tr>
</tbody>
</table>

**Clinical References:**

Hexosaminidase A, Serum

Clinical Information: Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 alterations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and a characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between ages 2 and 10 with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysartria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel that includes the most common genetic alterations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease (not detected by this test) is an autosomal recessive condition resulting from 2 alternations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing alteration. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have genetic alterations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural
substrate assay. Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with a high percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. However, not all individuals with this pattern are true carriers of Sandhoff disease, and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate (this test) does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Second-order test for diagnosing the B1 variant of Tay-Sachs disease This test is not useful for testing for Sandhoff disease.

**Interpretation:** Interpretation is provided with report. The B1 variant results in depressed Hex A isoenzyme as assayed by this test using the natural substrate, 4-methylumbelliferyl-beta-D-N-acetyl-glucosamine-6-sulfate (4-MUGS); whereas it reacts normally to the artificial substrate 4-MUG as assayed by NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes; NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, WholeÂ Blood; and NAGS / Hexosaminidase A and Total Hexosaminidase, Serum.

**Reference Values:**
- 1.23-2.59 U/L (normal)
- 1.16-1.22 U/L (indeterminate)
- 0.58-1.15 U/L (carrier)

**Clinical References:**

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**FSHAG**

**Hickory Shagbark (Carya ovata) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Å€â„¬å€œ 0.69 Low Positive 2 0.70 Å€â„¬å€œ 3.49 Moderate Positive 3 3.50 Å€â„¬å€œ 17.49 Positive 4 17.50 Å€â„¬å€œ 49.99 Strong Positive 5 50.00 Å€â„¬å€œ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
- <0.35 kU/L

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**HMGA**

**High Mobility Group A2 (HMGA2) Immunostain, Technical Component Only**

**Clinical Information:** High mobility group (HMG) proteins are nonhistone chromatin factors expressed during embryonic development that function to regulate transcription and cellular differentiation. When expression of HMGA2 is deregulated in cells of adult tissues, this oncofetal protein promotes neoplastic transformation. Abnormal HMGA2 expression has been observed in a wide variety of neoplasms, including uterine leiomyomas, ovarian serous carcinomas, lipomatous tumors, lymphangiomyomatosis, and pancreatic carcinomas. Normal spermatids express HMGA2. This immunostain may be useful in the differential diagnosis of lower genital tract mesenchymal tumors, showing positivity in the majority of aggressive angiomyxomas.
Useful For: Identification of abnormal expression of the high mobility group protein, HMGA2

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**HPLC 65615**

High-Performance Liquid Chromatography (HPLC)

**Hemoglobin Variant, Blood**

Clinical Information: A large number of variants of hemoglobin (Hb) have been recognized. Although many do not result in clinical or hematologic effects, clinical symptoms that can be associated with hemoglobin disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis/polycythemia, cyanosis/hypoxia, anemia (chronic, compensated or episodic), and increased methemoglobin or sulfhemoglobin results (M-hemoglobins). For common, and many of the uncommon, hemoglobin variants, protein studies will be sufficient for definitive identification. High-performance liquid chromatography is a method that provides useful and supplementary information on most hemoglobin variants.

Useful For: Providing additional information, which aids in the identification of hemoglobin variants

Interpretation: This test is not interpreted in isolation, but as a part of a profile.

Reference Values:
Only orderable as part of a profile. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation, Blood
- HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
- MEV1 / Methemoglobinemia Evaluation, Blood
- REVE1 / Erythrocytosis Evaluation, Whole Blood
- THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood


**HIPA 9756**

Hippuric Acid, Urine

Reference Values:
Reporting limit determined each analysis

Creatinine (mg/L):
U.S. Population (10th – 90th percentiles, median)
All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
Females: 273 - 2170 mg/L, median 994 (n=11,635)

Hippuric Acid (g/L)
Synonym(s): Hippurate; n-Benzoylglycine
Normal for unexposed populations is generally less than 1.6 g/L.

Hippuric Acid (Creatinine corrected) (g/g Creat)
Synonym(s): Hippurate; n-Benzoylglycine
Normal for unexposed populations is generally less than 1.5 g/g creatinine.

Specific Gravity Confirmation
Physiologic range: 1.010 - 1.030

FHSPL 57533 Histamine Plasma
Reference Values:
<1.0 ng/mL

FH24U 57821 Histamine, 24-Hour Urine
Clinical Information: Histamine is a mediator of the allergic response. Histamine release causes itching, flushing, hives, vomiting, syncope, and even shock. In addition, some patients with gastric carcinoids may exhibit high concentrations of histamine.

Reference Values:
Histamine, 24-hour Urine: 0.006 – 0.131 mg/24 h

Creatinine, 24-Hour Urine
Age (Years) g/24 hours
3-8 0.11 - 0.68
9-12 0.17 - 1.41
13-17 0.29 - 1.87
Adults 0.63 - 2.50

FHSTW 57368 Histamine, Whole Blood
Reference Values:
180 - 1800 nmol/L

HG34W 604697 Histone 3.3 G34W (H3F3A G34W) Immunostain, Technical Component Only
Clinical Information: H3F3A is a member of the histone H3 family and is located on chromosome 1. Histone H3 G34W is expressed in the nuclei of the mononuclear cell population of H3F3A altered giant cell tumor of bone (GCTB).

Useful For: Aiding in the diagnosis of giant cell tumor of bone
Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


HK27M 604989
Histone H3 K27M Mutant (H3 K27M) Immunostain, Technical Component Only

Clinical Information: Histone H3 K27M is an alteration in the H3F3A gene, encoding for histone H3.3. This alteration is characteristic of "diffuse midline glioma, H3 K27M-mutant," a new entity in the classification of central nervous system tumors, which carries a poor prognosis. H3 K27M-mutant diffuse midline glioma occurs most commonly in young children but, less frequently, can occur in adults. The most common locations include the brain stem, thalamus, and spinal cord. The term brain stem glioma and diffuse intrinsic pontine glioma (DIPG) were previously used to indicate tumors occurring in the brain stem and pons respectively.

Useful For: Identifying the presence of altered H3 K27M protein

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


HK36M 604699
Histone H3 K36M Mutant (H3F3 K36M) Immunostain, Technical Component Only

Clinical Information: H3F3B is a member of the histone H3 family and is located on chromosome 17. Histone H3 K36M is expressed in the nuclei of the mononuclear cell population of H3F3B altered chondroblastoma.
**Useful For:** Diagnosis of chondroblastoma

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**HISME 72127**

**Histone H3 Trimethyl K27 Immunostain, Technical Component Only**

**Clinical Information:** Histone H3 trimethyl-K27 is a bivalent epigenetic regulator that silences or represses the gene. Evaluation of H3 trimethyl-K27 immunohistochemical expression is a helpful biomarker in the diagnosis of diffuse midline gliomas H3 K27M-mutant, which most frequently occur in children and with less frequency in adults. These tumors typically occur along the midline and include intrinsic pontine gliomas (DIPG), thalamic, and spinal cord diffuse gliomas. H3 K27M mutations lead to global reduction in H3 trimethyl-K27 and result in H3 trimethyl-K27 loss of expression. Histologic mimics can be distinguishable from malignant peripheral nerve sheath tumors that show H3 trimethyl-K27 loss of expression.

**Useful For:** Diagnosis of malignant peripheral nerve sheath tumors and diffuse midline gliomas H3 K27M-mutant

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**SHSTO 26692**

**Histoplasma Antibody, Serum**

**Clinical Information:** Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and in immunosuppressed patients.
Useful For: Aiding in the diagnosis of active histoplasmosis using serum specimens

**Interpretation:** Complement fixation (CF) titers of 1:32 or higher indicate active disease. A rising CF titer is associated with progressive infection. Positive immunodiffusion test results supplement findings of the CF test. The simultaneous appearance of both H and M precipitin bands indicates active histoplasmosis. The M precipitin band alone indicates early or chronic disease or a recent histoplasmosis skin test. Patients infected with *Histoplasma capsulatum* demonstrate a serum antibody with a rising titer within 6 weeks of infection. A rising titer is associated with progressive infection. Specific antibody persists for a few weeks to a year, regardless of clinical improvement.

**Reference Values:**
- **MYCELIAL BY COMPLEMENT FIXATION (CF)**
  - Negative (positives reported as titer)

- **YEAST BY CF**
  - Negative (positives reported as titer)

- **ANTIBODY BY IMMUNODIFFUSION**
  - Negative (positives reported as band present)

**Clinical References:**

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**Histoplasma Antibody, Spinal Fluid**

**Clinical Information:** *Histoplasma capsulatum* is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and immunosuppressed patients.

**Useful For:** Aiding in the diagnosis of *Histoplasma* meningitis in spinal fluid specimens

**Interpretation:** Any positive serologic result in spinal fluid is significant. Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis.

**Reference Values:**
- **MYCELIAL BY COMPLEMENT FIXATION (CF)**
  - Negative (positives reported as titer)

- **YEAST BY CF**
  - Negative (positives reported as titer)

- **ANTIBODY BY IMMUNODIFFUSION**
  - Negative (positives reported as band present)

**Clinical References:**

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**Histoplasma Antigen, Random, Urine**

**Clinical Information:** *Histoplasma capsulatum* is a dimorphic fungus endemic to the Midwestern United States, particularly along the Mississippi River and Ohio River valleys. Infection occurs following inhalation of fungal microconidia and subsequent clinical manifestations are largely
dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk for severe infection include those with impaired cellular immunity, patients who have undergone organ transplantation, are HIV positive, or have a hematologic malignancy. The available laboratory methods for the diagnosis of H capsulatum infection include fungal culture, molecular techniques, serologic testing, and antigen detection. While culture remains the gold standard diagnostic test and is highly specific, prolonged incubation is often required and sensitivity decreases (9%-34%) in cases of acute or localized disease. Similarly, molecular methods offer high specificity, but decreased sensitivity. Serologic testing likewise offers high specificity; however, results may be falsely negative in immunosuppressed patients or those who present with acute disease. Also, antibodies may persist for years following disease resolution, thereby limiting the clinical specificity. Detection of H capsulatum antigen from urine samples has improved sensitivity (80%-95%) for the diagnosis of active histoplasmosis compared to both culture and serology. Additionally, urine antigen levels can be followed to monitor patient response to therapy, with declining levels consistent with disease resolution. Notably, however, H capsulatum antigen may persist at low levels following completion of antifungal therapy and clinical improvement.

**Useful For:** Aiding in the diagnosis of Histoplasma capsulatum infection Monitoring Histoplasma antigen levels in urine

**Interpretation:** Presence of Histoplasma antigen in urine is indicative of current or recent infection with Histoplasma capsulatum. Declining levels of Histoplasma antigen are indicative of disease regression and can be used to monitor patient response to antifungal therapy. Notably, low-level titers may persist for extended periods of time following appropriate treatment and resolution of infection. Urine samples with "Indeterminate" results are automatically reflexed to MiraVista Diagnostics for supplemental testing. Clinical decisions regarding Histoplasma infection should not be based on an indeterminate result alone. Other laboratory findings, including Histoplasma serology, fungal culture, and molecular tests (eg, reverse transcription-polymerase chain reaction: RT-PCR) should be considered, alongside clinical presentation and exposure history, to confirm the diagnosis. The absence of detectable Histoplasma antigen in urine suggests the absence of infection. Repeat testing on a fresh urine sample if early acute Histoplasma infection is suspected. Notably, patients with acute pulmonary infection or in patients with otherwise localized disease, the Histoplasma urine antigen test may be negative.

**Reference Values:**

**HISTOPLASMA ANTIGEN RESULT**

Negative

**HISTOPLASMA ANTIGEN VALUE**

Negative: 0.00-0.10

Indeterminante: 0.11-1.10

Positive: > or =1.11


**Histoplasma capsulatum/Blastomyces species, Molecular Detection, PCR, Varies**

**Clinical Information:** Infections with Blastomyces dermatitidis and Histoplasma capsulatum cause a variety of clinical manifestations ranging from self-limited, mild pulmonary illness to potentially life-threatening, disseminated disease. Patients at risk for disseminated disease include neonates and immunosuppressed individuals, particularly those with AIDS, hematologic malignancies, or a recent transplant. Primary infections are acquired through inhalation of microconidia that are present in the

**HB**

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800-533-1710 or 507-266-5700 or mayocliniclabs.com
environment. In the United States, most cases of blastomycosis and histoplasmosis occur along the Ohio and Mississippi River valleys. The gold standard for diagnosis of blastomycosis and histoplasmosis remains isolation of the organisms in culture. Although sensitive, recovery in culture and subsequent identification may require days to weeks. The organisms can be identified after growth in culture using traditional macro- and microscopic morphologic techniques or through the use of nucleic acid hybridization probes. Hybridization probe-based procedures are rapid and demonstrate good sensitivity and specificity from culture, although some cross-reactivity with relatively uncommon fungal organisms has been reported. Additional diagnostic tests that can be utilized for these organisms include stains, histopathology, serology, and antigen detection with each of these methods offering advantages and limitations depending on the stage of the illness and the status of the patient. Fungal stains (e.g., calcofluor white) offer a rapid diagnostic approach, but demonstrate poor sensitivity and specificity. Serologic tests such as complement fixation and immunodiffusion are noninvasive, but are laborious, subjective, and may show low sensitivity, especially in immunocompromised hosts. Antigen detection also offers a noninvasive approach, but has been demonstrated to show cross-reactivity with antigens from closely related fungal species. Molecular techniques have been established as sensitive and specific methods for the diagnosis of infectious diseases and have the added advantage of a rapid turnaround time for results. Due to the limitations of conventional diagnostic methods for blastomycosis and histoplasmosis, a single tube, real-time PCR assay was developed and verified for the detection and differentiation of B. dermatitidis/gilchristii and H. capsulatum directly from clinical specimens.

**Useful For:** Rapid detection of Histoplasma capsulatum and Blastomyces dermatitidis DNA. An aid in the rapid diagnosis of histoplasmosis and blastomycosis

**Interpretation:** A positive result for Histoplasma capsulatum indicates presence of Histoplasma DNA; a positive result for Blastomyces dermatitidis/gilchristii indicates presence of Blastomyces DNA. A negative result indicates absence of detectable H. capsulatum and B. dermatitidis/gilchristii DNA.

Fungal culture has increased sensitivity over this PCR assay and should always be performed when the PCR is negative.

**Reference Values:**
Not applicable


**HICBL 113132**

**Histoplasma/Blastomyces Panel, Spinal Fluid**

**Clinical Information:** Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and immunosuppressed patients. Blastomyces The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease: cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

**Useful For:** Aiding in the diagnosis of Histoplasma meningitis. Detecting antibodies in patients having blastomycosis

**Interpretation:** Histoplasma: -Any positive serologic result in spinal fluid is significant. -Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. -The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis. Blastomyces: A positive result is suggestive of infection, but the results cannot distinguish between active disease and
prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production, or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

**Reference Values:**
**Histoplasma ANTIBODY**
- Mycelial by complement fixation: Negative
- Yeast by complement fixation: Negative
- Antibody by immunodiffusion: Negative

**Blastomyces ANTIBODY IMMUNODIFFUSION**
Negative

**Clinical References:**

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**HIV Antigen and Antibody Prenatal Routine Screen, Plasma**

**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa and has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods.

**Useful For:** Screening for HIV-1 and/or HIV-2 infection in nonsymptomatic pregnant patients. This test is not offered as a screening or confirmatory test for blood donor specimens.

**Interpretation:** Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 infection is suspected, detection of HIV-1 RNA (HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. The following algorithms are available in Special Instructions: -HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results -HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results
Reference Values:
Negative


HIV-1 and HIV-2 Antibodies for Cadaveric or Hemolyzed Specimens, Serum

Clinical Information: Epidemiological data indicate that AIDS is caused by at least 2 types of HIV. The first virus, HIV-1, has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. They may fall into undetectable levels in the terminal stage of AIDS. See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HIV infection This test is not offered as a screening or confirmatory test for blood donor specimens.

Interpretation: A reactive HIV-1/-2 antibody screen result obtained by enzyme immunoassay (EIA) suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/-2 antibody EIA screen result usually indicates the absence of HIV-1 or HIV-2 infection. However, for specimens that are reactive by the rapid HIV antibody tests, confirmatory testing is recommended even if the EIA results are negative.

Reference Values:
Negative

HIV-1 and HIV-2 Antibody Confirmation and Differentiation
Prenatal, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in plasma specimens from prenatal patients who show reactive results with 3rd- (HIV-1/-2 antibody only) and 4th-generation (HIV antigen and antibody) HIV serologic assays. This test is not useful as a screening test for HIV infection in symptomatic or asymptomatic individuals. This test is not to be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. In this situation, the HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma reflex test will be performed. For patients at risk for HIV-2 infection (eg, having lived in West Africa or have sexual partners from West Africa), testing for HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended. Positive HIV-1 antibody but negative HIV-2 antibody results indicate the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma is recommended to verify and confirm the diagnosis of HIV-1 infection prior to initiating antiretroviral treatment. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection, with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Submit a new plasma specimen for detection of HIV-1 RNA (HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma). However, such result patterns may rarely indicate early HIV-2 infection (ie, HIV-2 coinfection) in HIV-1-infected individuals. For individuals at risk for HIV-2 infection (based on epidemiologic exposure history), a whole blood specimen should be submitted also for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. In this situation, the HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma reflex test will be performed. Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, may be due to acute HIV-1 infection or suggests either very early HIV-2 infection (in individuals with risk factors) or presence
of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. In this situation, the HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma reflex test will be performed. If the subsequent HIV-1 RNA test result is negative and patient has known risk factors for HIV-2 infection (based on the patient's clinical and epidemiologic history), a new whole blood specimen should be submitted for detection of FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Positive results for both HIV-1 and HIV-2 antibodies suggest probable presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to: a) HIV-1 infection with HIV-2 antibody cross-reactivity; or b) HIV-2 infection with HIV-1 antibody cross-reactivity (eg. absence of HIV-1 p24 and p31 bands).

Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. Based on the patient's clinical and epidemiologic history, a new plasma specimen should be submitted for detection of HIV-1 RNA (HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma) and a new whole blood specimen for detection of HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR). Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). In this situation, the HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma reflex test will be performed. Negative HIV-1 antibody but positive HIV-2 antibody results indicates the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg. presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection.

Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. If the patient is at risk for HIV-1 infection (based on the patient's clinical and epidemiologic history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIQNP / HIV-1 RNA Detection and Quantification Prenatal, Plasma). Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. However, such result patterns may rarely indicate early HIV-1 infection (ie, HIV-1 coinfection) in HIV-2-infected individuals. For individuals at risk for HIV-1 infection, (based on epidemiologic exposure history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma). The following algorithms are available in Special Instructions: HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results -HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results

Reference Values:

Negative

HIV-1 and HIV-2 Antibody Confirmation and Differentiation, Plasma

**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Confirmation and differentiation of HIV-1 and HIV-2 antibodies in plasma specimens that show reactive results with third-(HIV-1/-2 antibody only) and 4th-generation (HIV antigen and antibody) HIV serologic assays. This test is not useful as a screening test for HIV infection in symptomatic or asymptomatic individuals. This test is not to be used as a screening or confirmatory test for blood donor specimens.

**Interpretation:** Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. In this situation, the HIVQN / HIV-1 RNA Detection and Quantification, Plasma reflex test will be performed. For patients at risk for HIV-2 infection (eg, having lived in West Africa or have sexual partners from West Africa), testing for HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended. Positive HIV-1 antibody, but negative HIV-2 antibody results, indicates the presence of HIV-1 infection, together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIVQN / HIV-1 RNA Detection and Quantification, Plasma is recommended to verify and confirm the diagnosis of HIV-1 infection prior to initiating antiretroviral treatment. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection, with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Submit a new plasma specimen for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma). However, such result patterns may rarely indicate early HIV-2 infection (ie, HIV-2 coinfection) in HIV-1-infected individuals. For individuals at risk for HIV-2 infection (based on epidemiologic exposure history), a whole blood specimen should be submitted also for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. In this situation, the HIVQN / HIV-1 RNA Detection and Quantification, Plasma reflex test will be performed. Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, may be due to acute HIV-1 infection or suggests either very early HIV-2 infection (in individuals with risk factors) or presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. In this situation, the HIVQN / HIV-1 RNA Detection and Quantification, Plasma reflex test will be performed. If the subsequent HIV-1 RNA test result is negative and the patient has known risk factors for HIV-2 infection (based on the patient's clinical and epidemiologic history), a new whole blood specimen should be submitted for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR detection. Positive results for both
HIV-1 and HIV-2 antibodies suggest probable presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to: a) HIV-1 infection with HIV-2 antibody cross-reactivity; or b) HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. Based on the patient's clinical and epidemiologic history, a new plasma specimen should be submitted for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) and a new whole blood specimen for detection of HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR). Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients’ specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). In this situation, the HIVQN / HIV-1 RNA Detection and Quantification, Plasma reflex test will be performed. Negative HIV-1 antibody but positive HIV-2 antibody results indicates the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. If the patient is at risk for HIV-1 infection (based on patient's clinical and epidemiologic history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma). Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. However, such result patterns may rarely indicate early HIV-1 infection (ie, HIV-1 coinfection) in HIV-2-infected individuals. For individuals at risk for HIV-1 infection, (based on epidemiologic exposure history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma). See HIV Testing Algorithm (Fourth Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

Reference Values:
Negative


HV1CM 60357

HIV-1 and HIV-2 Antibody Screen for Hemolyzed Specimens, Serum

Clinical Information: Epidemiological data indicate that AIDS is caused by at least 2 types of
HIV. The first virus, HIV-1, has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. They may fall into undetectable levels in the terminal stage of AIDS. See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

**Useful For:** Screening cadaveric or hemolyzed serum specimens for HIV-1 and/or HIV-2 infection in non-symptomatic patients with or without risk factors for HIV infection This test is not offered as a screening or confirmatory test for blood donor specimens.

**Interpretation:** A reactive HIV-1/-2 antibody screen result obtained by enzyme immunoassay (EIA) suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/-2 antibody EIA screen result usually indicates the absence of HIV-1 or HIV-2 infection. However, for specimens that are reactive by the rapid HIV antibody tests, confirmatory testing is recommended even if the EIA results are negative.

**Reference Values:**
Negative

**Clinical References:**

**HIVDX 48392**

**HIV-1 and HIV-2 Antigen and Antibody Diagnostic Evaluation, Plasma**

**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only
for specimens that are repeatedly reactive by these methods.

**Useful For:** Diagnosing HIV-1 and/or HIV-2 infection in symptomatic patients more than 2 years old. Follow-up testing of individuals with reactive rapid HIV test results. This test is not offered as a screening or confirmatory test for blood donor specimens.

**Interpretation:** Negative HIV-1/-2 antigen and antibody screening test results usually indicate the absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 infection is suspected, detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) or HIV-1 DNA and RNA (HIVP / HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

**Reference Values:**
Negative

**Clinical References:**
Useful For: Screening for HIV-1 and HIV-2 infection in nonsymptomatic, nonpregnant individuals older than 2 years. This test is not offered as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 infection is suspected, detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) or HIV-1 DNA and RNA (HIVP / HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as the HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

Reference Values:
Negative

Clinical References:

HIVP
64693

HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma

Clinical Information: Human immunodeficiency virus (HIV)-1 infection is usually confirmed by detection of HIV-1-specific antibodies in serum. However, serologic testing may not reliably identify HIV-1 infection in neonates with passively acquired maternal HIV-1 antibodies or with incompletely developed immune systems, individuals with early HIV-1 infection (<30 days from infection), or individuals with "indeterminate" HIV-1 antibody results by supplemental serologic assays. In these situations, detection of HIV-1 nucleic acids (RNA or proviral DNA) by PCR can provide definitive, early evidence of HIV-1 infection (approximately 10 to 14 days after infection), when results of routine diagnostic assays may be inconclusive. Upon entry into human cells (including peripheral blood mononuclear cells), the HIV-1 RNA is converted into complementary DNA (cDNA) by reverse transcription. These linear cDNA strands are then integrated into the host cell genome, thus representing the proviral form of HIV-1. mRNA, transcribed from the proviral DNA, is used to synthesize the proteins required to make new viral particles. These proteins and viral RNA are packaged in the host's cytoplasm and released from the cell, completing the life cycle of the virus. For infants born to HIV-1-infected mothers, HIV-1 DNA or RNA tests are recommended at 0 to 2 days, 14 days, 1 to 2 months, and 4 to 6 months after birth. Two consecutive positive HIV-1 virologic test results (HIV-1 DNA and/or RNA) are necessary for confirming the diagnosis of HIV-1 infection in infants younger than 2 years of age.

Useful For: Virologic detection of HIV-1 infection in infants younger than 2 years of age (an age
Interpretation: A "Detected" result is consistent with HIV infection (see Cautions). Per CDC and US Public Health Services recommendations, a second specimen should be collected from any patient with first-time detectable HIV-1 DNA or RNA result and tested to verify the diagnosis of HIV-1 infection. An "Undetected" result indicates that neither HIV-1 DNA nor RNA is detected in the specimen (see Cautions). Repeat testing is recommended at 0 to 2 days, 14 days, 1 to 2 months, and 4 to 6 months after birth in infants born to HIV-1-infected mothers. For at-risk individuals older than 2 years of age, repeat testing in 1 to 2 months is recommended. The lower limits of detection (based on 95% detection rate) of this assay in plasma are 311 copies/mL for HIV-1 DNA and 75 copies/mL for HIV-1 RNA. An "Inconclusive" result indicates that the absence or presence of HIV-1 DNA or RNA could not be determined with certainty after repeat testing of the clinical specimens in the laboratory, possibly due to PCR inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References:

HIVPR

HIV-1 Genotypic Drug Resistance to Protease and Reverse Transcriptase Inhibitors, Plasma

Clinical Information: Antiviral resistance may compromise highly active antiretroviral therapy (HAART) in HIV-infected patients receiving HAART. When combination therapy fails, detection and analysis of HIV genotypic variants can guide necessary changes to antiretroviral therapy and decrease HIV viral load, thereby improving patient outcome. HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA (cDNA) by the action of the viral reverse transcriptase (RT) gene product. RT has little proofreading capacity and therefore, incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease catalyzes a polypeptide to produce peptides necessary for active viral replication. Although HAART (combination of nucleoside analog, nonnucleoside agent and/or protease inhibitor) may be effective in reducing the viral load, genotypic variants arising in the drug-targeted HIV gene loci due to selective pressure from antiviral therapy result in antiviral resistance that may compromise such therapy. Amplification and analysis of drug-targeted HIV-gene sequence allows identification of changes in nucleotide bases and associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are deemed as variants by comparing the sequence data of the patient's HIV strain to those of a wild-type HIV strain. The significance of these genotypic variants in relation to antiviral resistance is then determined by a set of interpretive rules developed by a consensus panel of leading experts in the field of HIV resistance. Relevant data presented at a recognized scientific conference or published in peer-reviewed journals are considered by the consensus panel in developing these rules. When necessary, reliable unpublished drug resistance data known to
consensus panel members may be considered in the process. The interpretive rules are updated by the consensus panel annually after reviewing newly published data on HIV-1 genotypic drug resistance variants.

**Useful For:** Identification of genotypic variants associated with viral resistance to HIV-1 nucleotide reverse-transcriptase inhibitors, non-nucleotide reverse-transcriptase inhibitors, and protease inhibitors

Guiding initiation or change of combination antiretroviral therapy in individuals, including children, living with HIV

**Interpretation:** Detectable HIV-1 genotypic variants conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, M184V) resulting from the alterations, according to the interpretative algorithm of the Stanford HIV Database program. Genotypic variant codons are categorized and interpreted in relation to previously performed phenotypic antiviral susceptibility tests. Each variant is assigned a drug penalty score and the total score generated from all of the variants relevant to the specific antiviral drug is used to estimate the level of resistance to that drug. These interpretive rules may be updated periodically by the Stanford HIV Database Team after reviewing newly published data on HIV-1 genotypic drug resistance variants. Susceptible (SUSC) indicates that the genotypic variants present in patient's HIV-1 strain have not been associated with resistance to the specific drug (Stanford HIVdb total score 0 to 9). Potential Low-Level Resistance (PLR) indicates that genotypic variants detected have been associated with possible reduction in susceptibility to the specific drug (Stanford HIVdb score 10 to 14). Low-Level Resistance (LR) indicates that genotypic variants detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 15 to 29). Intermediate Resistance (IR) indicates that genotypic variants detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 30 to 59). High-level Resistant (HR) indicates that genotypic variants detected have been associated with maximum reduction in susceptibility to the specific drug (Stanford HIVdb > or = 60). Unable to genotype indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant variants in the patient's HIV strain. Probable causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction, or low viral load (ie, <500 copies/mL). Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of the presence of PCR inhibitors or ambiguous or incomplete viral target sequences generated from the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**HIV-1 Genotypic Integrase Inhibitor Drug Resistance, Plasma**

**Clinical Information:** Antiviral resistance may compromise highly active antiretroviral therapy (HAART) in HIV-1-infected patients receiving HAART. When combination therapy fails, detection and analysis of HIV genotypic mutations can guide necessary changes to antiretroviral therapy and decrease HIV-1 viral load, thereby improving patient outcome. HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA (cDNA) by the action of the viral reverse transcriptase (RT). RT has little proofreading capacity and therefore incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease (PR) catalyzes a polyprotein to produce peptides necessary for active viral replication. Although HAART (combinations of nucleoside analogs, nonnucleoside agents, protease inhibitors and/or integrase strand transfer inhibitors) may be effective in reducing viral load, genotypic mutations arising in
drug-targeted HIV loci due to selective pressure from antiviral therapy can result in antiviral resistance that may compromise such therapy. Amplification and analysis of drug-targeted HIV-1 sequences allows identification of changes in nucleotide sequence and associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are identified by comparing the sequence data of the patient's HIV-1 strain to that of a wild-type HIV-1 strain. The significance of these genotypic mutations in relation to antiviral resistance is then determined by a set of interpretive rules developed and used by the Stanford HIVdb Program Genotypic Resistance Interpretation Algorithm (http://sierra2.stanford.edu/sierra/servlet/JSierra) for final interpretation. In the Stanford HIVdb program, genotypic mutations are categorized and interpreted according to phenotypic antiviral susceptibility tests performed using the ViroLogic PhenoSense assay (Monogram Biosciences Inc, San Francisco, US) or a HeLa-CD4 reporter gene assay. Each mutation is assigned a drug penalty score and the total score generated from all of the mutations relevant to the specific antiviral drug is used to estimate the level of resistance to that drug. These interpretive rules may be updated periodically by the Stanford HIVdb Team after reviewing newly published data on HIV-1 genotypic drug resistance mutations.

**Useful For:** Identification of HIV-1 genotypic mutations in the integrase region of HIV-1 to predict antiretroviral drug resistance in HIV-1-infected patients receiving integrase strand transfer inhibitors (ie, bictegravir, dolutegravir, elvitegravir, raltegravir) Guiding initiation or change of drug combinations for the treatment of HIV-1 infection

**Interpretation:** Detectable HIV-1 genotypic mutations conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, N155H), along with associated resistance interpretations for the current FDA-approved integrase strand transfer inhibitors (bictegravir, dolutegravir, elvitegravir, and raltegravir). Susceptible (SUSC) indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug (Stanford HIVdb total score 0 to 9). Potential Low-Level Resistance (PLR) indicates that genotypic mutations detected have been associated with possible reduction in susceptibility to the specific drug (Stanford HIVdb score 10 to 14). Low-Level Resistance (LR) indicates that genotypic mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 15 to 29). Intermediate Resistance (IR) indicates that genotypic mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 30 to 59). High-level Resistance (HR) indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug (Stanford HIVdb score > or =60). Unable to Genotype indicates that viral target sequences are of poor quality to reliably determine antiviral resistance. This result may be due to low viral load, ambiguous or incomplete viral target sequences, presence of PCR inhibitors, and/or mutations in the PCR or sequencing primer binding regions. Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of the presence of PCR inhibitors, mutations in the PCR or sequencing primer binding regions, or ambiguous or incomplete viral target sequences that did not allow reliable analysis to determine antiviral resistance.

**Reference Values:**
Not applicable

asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of individuals living with HIV-1. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 2 years of age, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the U.S. Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends use of HIV RNA or proviral DNA tests for the detection of HIV infection in infants born to HIV-infected mothers.

**Useful For:**
- Diagnosis of HIV-1 infection in individuals with acute or early HIV-1 infection
- Diagnosis of HIV-1 infection in infants under 2 years of age born to mothers living with HIV-1
- Quantifying plasma HIV-1 RNA levels (viral load) in individuals living with HIV-1:
  - Before initiating anti-HIV-1 drug therapy (baseline viral load)
  - Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy
  - Who may be noncompliant with anti-HIV-1 drug therapy
- Monitoring HIV-1 disease progression before or during antiretroviral drug therapy

**Interpretation:** This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-negative). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

**Reference Values:**
- Undetected

**Clinical References:**
HIV-1 RNA Detection and Quantification, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 18 months of age, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the United States Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends use of proviral DNA or RNA tests for the detection of HIV infection in infants born to HIV-infected mothers.(1)

Useful For: Diagnosis of HIV-1 infection in individuals with acute or early HIV-1 infection Diagnosis of HIV-1 infection in infants of under 18 months of age born to HIV-1-infected mothers Quantifying plasma HIV-1 RNA levels (viral load) in HIV-1-infected individuals: -Before initiating anti-HIV-1 drug therapy (baseline viral load) -Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy -Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression while on or off antiretroviral drug therapy

Interpretation: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, less than 3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

Reference Values:
Undetected

**HIV-1 RNA Detection and Quantification, Prenatal, Plasma**

**Clinical Information:** Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients.

**Useful For:** Diagnosis of HIV-1 infection in pregnant individuals with acute or early HIV-1 infection

Quantifying plasma HIV-1 RNA levels (viral load) in pregnant individuals living with HIV-1: -Before initiating anti-HIV-1 drug therapy (baseline viral load) -Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy -Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression before or during antiretroviral drug therapy in pregnant individuals

**Interpretation:** This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load <20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

**Reference Values:**

Undetected

HIV-1 RNA Quantification with Reflex to HIV-1 Genotypic Drug Resistance to Protease and Reverse Transcriptase Inhibitors, Plasma

Clinical Information: HIV-1 is an RNA virus that infects human host cells and is then converted to complementary DNA (cDNA) by the action of viral reverse transcriptase. HIV-1 is the causative agent of AIDS, a severe, life-threatening condition. Currently, 2 types of HIV: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for over 99% of HIV infections in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. Studies have identified a number of mutations associated with antiviral resistance. Genotypic analysis allows identification of nucleotide changes associated with HIV drug resistance. When combination therapy fails, genotyping for drug resistance mutations may help direct appropriate changes in antiretroviral therapy and may result in at least a short-term benefit, as evidenced by viral load reduction.

Useful For: Quantifying plasma HIV-1 RNA levels (viral load) in individuals living with HIV, including children, followed by identification of genotypic mutations associated with viral resistance to inhibitors of HIV-1 reverse transcriptase and protease Guiding initiation or change of combination antiretroviral therapy in individuals, including children, living with HIV

Interpretation: HIRGT: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA within the plasma specimen. A result of "<20 IU/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, less than 3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of greater than 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-to-drug interactions, and patient adherence. If the viral load is greater than or equal to 500 copies/mL, genotypic antiviral drug resistance mutation analysis is performed automatically at an additional charge. HIVPR: Codon sequences of the patient's HIV-1 reverse transcriptase and protease genes are compared with those in a database of known antiretroviral drug resistance mutations provided in the assay manufacturer's software application. Results are provided that highlight those codon changes
associated with specific drug resistance. These mutations are categorized and reported. "Susceptible (SUSC)" indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug in question. "Resistant (RESIST)" indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug. "Possible resistance (PR)" indicates that genotypic mutations detected have been associated with 1 or both of the following outcomes: -Diminished virologic response in some, but not all, patients having virus with these mutations -Intermediate decrease in susceptibility of the virus to the specific drug "Unable to genotype" result indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient's HIV strain. Probable causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction, or low viral load (ie, <500 copies/mL). "Inconclusive" result indicates inability of the assay to reliably determine antiviral resistance because of the presence of PCR inhibitors or ambiguous or incomplete viral target sequences generated from the assay.

Reference Values:
Undetected

Clinical References:

HIV-1 RNA Quantification with Reflex to HIV-1 Genotypic Drug Resistance, Plasma

Clinical Information: HIV-1 is an RNA virus that infects human host cells and is then converted to complementary DNA (cDNA) by the action of viral reverse transcriptase. HIV-1 is the causative agent of AIDS, a severe, life-threatening condition. Currently, 2 types of HIV: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for over 99% of HIV infections in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. Studies have identified a number of mutations associated with antiviral resistance. Genotypic analysis allows identification of nucleotide changes associated with HIV drug resistance. When combination therapy fails, genotyping for drug resistance mutations may help direct appropriate changes in antiretroviral therapy and may result in at least a short-term benefit, as evidenced by viral load reduction.

Useful For: Detecting and quantifying plasma HIV-1 RNA levels (viral load) in HIV-1-infected patients, followed by genotypic determination of viral resistance to anti-HIV drugs Guiding initiation or
change of antiretroviral treatment regimens

**Interpretation:** HIV-1 Detection and Quantification: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA within the plasma specimen. A result of "<20 IU/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-to-drug interactions, and patient adherence. Genotypic anti-HIV-1 drug resistance mutation analysis is performed automatically at an additional charge if the viral load is 500 copies/mL or above. Sequence data of the patient's viral strain is compared with those in a database of known drug resistance mutations. Results are provided that highlight those codon changes associated with specific drug resistance. These mutations are categorized and reported. HIV-1 Genotypic Drug Resistance Analysis: "Susceptible" indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug in question. "Resistant" indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug. "Possible resistance" indicates that genotypic mutations detected have been associated with I or both of the following outcomes: -Diminished virologic response in some, but not all, patients having virus with these mutations -Intermediate decrease in susceptibility of the virus to the specific drug "Unable to genotype" indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient's HIV strain. Possible causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction. "Inconclusive" indicates inability of the assay to reliably determine antiviral resistance because of either low HIV-1 viral load (ie, <500 copies/mL) or ambiguous or incomplete viral target sequences generated from the assay.

**Reference Values:**
Undetected


**HIV2L**

**HIV-2 Antibody Confirmation, Serum**

**Clinical Information:** Human immunodeficiency virus type 2 (HIV-2) is a lentivirus, a retrovirus in the same genus (Lentiviridae) as HIV-1. It was first isolated in 1986 in West Africa, where it is currently endemic. As of June 2010, CDC has reported a total of 166 cases that met the CDC case definition of HIV-2 infection in the United States. Most of these cases were found in the northeastern United States, and the majority had a West African origin or connection. Compared to HIV-1 infection, HIV-2 infection is associated with slower rate of progression, low viral load (which may not be reliably
measured with current methods), slower rates of decline in CD4 cell count, and lower rates of transmission (sexually or vertically). Up to 95% of HIV-2-infected individuals are long-term nonprogressors, and individuals with undetectable HIV-2 viral load have similar survival rates as that of the uninfected population. However, HIV-2 does cause immunosuppression as well as AIDS with the same signs, symptoms, and opportunistic infections seen in HIV-1. Due to the rarity of HIV-2, there are scant data from controlled trials to inform management decisions. Although there are several FDA-approved screening assays to detect combined HIV-1 and HIV-2 antibodies or HIV-2 antibodies alone, currently there is only one FDA-approved supplemental (confirmatory) HIV-2 serologic assay for clinical use in the United States.

**Useful For:** Confirmation of the presence of HIV-2 antibodies in patients with repeatedly reactive combined HIV-1 and HIV-2 antibody or HIV-2 antibody-only screening test results Diagnosis of HIV-2 infection

**Interpretation:** Negative results for HIV-2 antibodies usually indicate the absence of HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV-2 infection. If acute or early HIV-2 infection is suspected, detection of HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended, based on the patient's clinical and epidemiologic exposure history. Positive HIV-2 antibody results indicate the presence of HIV-2 infection. Additional testing with a new whole blood specimen for HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Indeterminate HIV-2 antibody results may be due to acute HIV-1 infection or very early HIV-2 infection (in individuals with risk factors). If acute HIV-1 infection or early HIV-2 infection is suspected, detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) and/or HIV-2 DNA/RNA (FHV2Q / HIV-2 HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended, depending on the epidemiologic exposure history.

**Reference Values:**
Negative


**FHV2Q**

**Reference Values:**
Reference Range: Not Detected

**FHLAA**

**Reference Values:**
Testing is complete. Final report has been sent to the referring laboratory.
HLA-B*57:01 Genotype, Pharmacogenomics, Varies

**Clinical Information:** The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1500 different HLA-B alleles identified, one of which is the HLA-B*57:01 allele. Frequency of the HLA-B*57:01 allele varies with ethnicity, with a frequency of 6% to 7% in European populations and up to 20% in Southwest Asian populations. The HLA-B*57:01 allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the HLA-B*57:01 allele are at an increased risk for abacavir hypersensitivity, and it is not recommended for use in treating these individuals. Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the HLA-B*57:01 genotype and excluding HLA-B*57:01-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity. Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy. In clinical trials with pazopanib, hepatotoxicity was observed, manifested as increases in serum transaminases such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Patients who are HLA-B*57:01 carriers and are taking pazopanib are at increased risk of elevated ALT levels.(1,2) According to the FDA label for pazopanib, in an analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, elevation in ALT to levels greater than 3 times the upper limit of normal occurred in 32% (42/133) of HLA-B*57:01 allele carriers as compared to 19% (397/2101) of noncarriers. Furthermore, elevation in ALT to levels greater than 5 times the upper limit of normal occurred in 19% (25/133) of HLA-B*57:01 allele carriers and in 10% (213/2101) of noncarriers. All patients taking pazopanib should have hepatic function monitored, regardless of HLA-B*57:01 carrier status, and administration of pazopanib should be interrupted, reduced, or discontinued according to recommendations in the FDA label if hepatic function is impaired. UGT1A1 genotype is also relevant to pazopanib-induced hyperbilirubinemia and testing may also be warranted. See U1A1V / UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, UGT1A1, Varies.

**Useful For:** Identifying individuals with an increased risk of hypersensitivity reactions to abacavir, based on the presence of the human leukocyte antigen HLA-B*57:01 allele. Identifying individuals taking pazopanib who have an increased risk of elevated alanine aminotransferase (ALT) levels based on the presence of the human leukocyte antigen HLA-B*57:01 allele.

**Interpretation:** Positivity for human leukocyte antigen allele HLA-B*57:01 confers high risk for hypersensitivity to abacavir and higher risk of elevated alanine aminotransferase (ALT) levels in patient taking pazopanib. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. For additional information regarding pharmacogenomic genes and their associated...
Reference Values:
Negative
An interpretive report will be provided.

Clinical References:

Clinical Information:
The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1500 different HLA-B alleles identified, one of which is the HLA-B*58:01 allele. The frequency of the HLA-B*58:01 allele varies with ethnicity, with a frequency of 10% to 17% in Han Chinese, 6% in Korean, 6% to 8% in Thai, and 3% to 6% in African American populations. This allele is present at a lower frequency (approximately 1%-2%) among the white and Hispanic populations. Allopurinol is a drug widely used for hyperuricemia-related diseases such as gout, Lesch-Nyhan syndrome, and recurrent urate kidney stones. Allopurinol has been associated with severe cutaneous adverse reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and allopurinol hypersensitivity syndrome (AHS). These reactions have a reported mortality rate of 20% to 25%. The HLA-B*58:01 allele is associated with a markedly elevated risk for SCAR/AHS. Guidelines from the Clinical Pharmacogenomics Implementation Consortium (CPIC) recommend HLA-B*58:01 genotyping be performed when considering prescribing allopurinol, and that allopurinol should not be prescribed to patients who test positive for the allele due to the increased risk of SCAR. In addition, the 2020 American College of Rheumatology Guideline for the Management of Gout recommends testing for the HLA-B*58:01 allele prior to initiation of allopurinol in patients of Southeast Asian descent (eg, Han Chinese, Korean, Thai) and for African American patients.

Useful For: Identifying individuals with an increased risk of severe cutaneous adverse reactions to allopurinol based on the presence of the human leukocyte antigen HLA-B*58:01 allele

Interpretation: Positivity for HLA-B*58:01 confers increased risk for hypersensitivity to allopurinol. For additional information regarding pharmacogenic and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

**LY27B HLA-B27, Blood**

**Clinical Information:** This major histocompatibility coded class I antigen is associated with ankylosing spondylitis, juvenile rheumatoid arthritis, and Reiter syndrome. The mechanism of the association is not understood but probably is that of linkage disequilibrium. There is an increased prevalence of HLA-B27 in certain rheumatic diseases, particularly ankylosing spondylitis. Studies have demonstrated that the B*27:06 allele, which is present in a small percentage of individuals of Asian ethnicity, may not be associated with ankylosing spondylitis.

**Useful For:** Assisting in the diagnostic process of ankylosing spondylitis, juvenile rheumatoid arthritis, and Reiter syndrome

**Interpretation:** Approximately 8% of the normal population carries the HLA-B27 antigen. HLA-B27 is present in approximately 89% of patients with ankylosing spondylitis, 79% of patients with Reiter syndrome, and 42% of patients with juvenile rheumatoid arthritis. However, lacking other data, it is not diagnostic for these disorders.

**Reference Values:** An interpretive report will be provided.


**HMB45 Immunostain, Technical Component Only**

**Clinical Information:** The HMB45 immunostain identifies an antigen that is associated with a premelanosomal glycoprotein found in activated and neoplastic melanocytes. Most melanomas (approximately 90%) react with HMB45. HMB45 staining is cytoplasmic and is usually diffuse but may be focal. Benign nevi (moles) and other tumors that have melanin production (such as peripheral nerve sheath tumors) also stain positively.

**Useful For:** Identification of activated and neoplastic melanocytes

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:** 1. Uguen A, Uguen M, Guibourg B, Talagas M, Marcarelles P, De Braekeleer M: The p16-Ki-67-HMB45 immunohistochemistry scoring system is highly concordant with the fluorescent in situ hybridization test to differentiate between melanocytic nevi and melanomas. Appl
**HMBSZ 35457**

**HMBS Gene, Full Gene Analysis, Varies**

**Clinical Information:** Hydroxymethylbilane synthase (HMBS) deficiency is an autosomal dominant disorder with incomplete penetrance that can present as acute intermittent porphyria (AIP). The most common clinical presentation of AIP is abdominal pain. Acute attacks can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HMBS deficiency can also be without clinical or biochemical manifestations. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco and cannabis. The measurement of porphobilinogen deaminase (PBG-D) enzyme activity in erythrocytes facilitates detection of AIP during latent periods, and also confirms a biochemical diagnosis during acute episodes. However, a normal result does not completely exclude a diagnosis of HMBS deficiency/AIP. The preferred diagnostic test is molecular genetic testing of the HMBS gene.

**Useful For:** Confirming a diagnosis of hydroxymethylbilane synthase deficiency/acute intermittent porphyria

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

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HCMM 89047**

**Homocysteine (Total), Methylmalonic Acid, and Methylcitric Acid, Blood Spot**

**Clinical Information:** Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, mental retardation, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine (free and total) along with decreased concentrations of cystine. Methylmalonic acidemia (MMA) and propionic acidemia (PA) are defects of propionate metabolism caused by deficiencies in methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMA includes elevations of propionyl carnitine, methylmalonic acid, and...
methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal methylmalonic acid concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Newborn screening for inborn errors of methionine and propionic acid metabolism relies on elevations of methionine and propionyl carnitine. These analytes are not specific for these conditions and are prone to false-positive results, leading to increased cost, stress, and anxiety for families who are subjected to follow-up testing. Homocysteine, methylmalonic acid, and methylcitric acid are more specific markers for inborn errors of methionine and propionic acid metabolism. Molecular genetic testing can be used to confirm a biochemical diagnosis for homocystinuria, methylmalonic acidemia, and propionic acidemia.

**Useful For:** Second-tier assay of newborn screening specimens when abnormal propionyl carnitine or methionine concentrations are identified in a primary newborn screen

**Interpretation:** Elevated homocysteine, methylcitric acid, or methylmalonic acid concentrations are indicative of an underlying metabolic disorder.

**Reference Values:**

**HOMOCYSTEINE:**

<9.0 nmol/mL

**METHYLMALONIC ACID:**

<4.0 nmol/mL

**METHYL CITRIC ACID:**

<1.0 nmol/mL

An interpretive report will also be provided.

**Clinical References:**


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**HCYSP 80379**

**Homocysteine, Total, Plasma**

**Clinical Information:** Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Genetic defects in vitamin cofactors (vitamins B6, B12, and folate) and nutritional deficiency of vitamin B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine was also thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to the year 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following U.S. Food and Drug Administration mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids, quantitative acylcarnitines, methylmalonic acid, and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine.
Useful For: An aid for screening patients suspected of having an inherited disorder of methionine metabolism including:
- Cystathionine beta-synthase deficiency (homocystinuria)
- Methylene-tetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants
- Methionine synthase deficiency
- Cobalamin (Cbl) metabolism
- Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies
- Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies
- Transcobalamin II deficiency
- Adenosylhomocysteinase (AHCY) deficiency
- Glycine N-methyltransferase (GNMT) deficiency
- Methionine adenosyltransferase (MAT) I/III deficiency

Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine metabolism
Evaluating individuals with suspected deficiency of vitamin B12 or folate

Interpretation: Elevated homocysteine concentrations are considered informative in patients evaluated for suspected nutritional deficiencies (vitamin B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between vitamin B12 (cobalamin) and folate deficiencies, as MMA is only elevated in vitamin B12 deficiency. Treatment response can be evaluated by monitoring plasma homocysteine concentrations over time.

Reference Values:

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| >85 years | 7.4 - 16.0            | 8.3 - 16.2                   

**Clinical References:**
pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Genetic defects in vitamin cofactors (vitamins B6, B12, and folate) and nutritional deficiency of vitamin B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine was also thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to the year 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following U.S. Food and Drug Administration mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids, quantitative acylcarnitines, methylmalonic acid, and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

**Useful For:** An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants: -Methionine synthase deficiency -Cobalamin (Cbl) metabolism -Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency -Adenosylhomocysteinate (AHCY) deficiency -Glycine N-methyltransferase (GNMT) deficiency -Methionine adenosyltransferase (MAT) I/III deficiency Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine metabolism Evaluating individuals with suspected deficiency of vitamin B12 or folate

**Interpretation:** Elevated homocysteine concentrations are considered informative in patients evaluated for suspected nutritional deficiencies (vitamin B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between vitamin B12 (cobalamin) and folate deficiencies, as MMA is only elevated in vitamin B12 deficiency. Treatment response can be evaluated by monitoring serum homocysteine concentrations over time.

**Reference Values:**

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1355
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<tr>
<td>&gt;85 years</td>
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**HVA**

**Homovanillic Acid, 24 Hour, Urine**

**Clinical Information:** Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid: [MA and dopamine] are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monoamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** Screening children for catecholamine-secreting tumors with a 24-hour urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

**Interpretation:** Vanillylmandelic acid (VMA) and/or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monoamine oxidase-A deficiency.

**Reference Values:**

- <1 year: <35.0 mg/g creatinine
- 1 year: <30.0 mg/g creatinine
- 2-4 years: <25.0 mg/g creatinine
- 5-9 years: <15.0 mg/g creatinine
- 10-14 years: <9.0 mg/g creatinine
- > or =15 years (adults): <8.0 mg/24 hours


**HVAR**

**Homovanillic Acid, Random, Urine**

**Current as of June 14, 2021 12:13 pm CDT**

800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Clinical Information:** Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid: VMA and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monoamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** Screening children for catecholamine-secreting tumors with a random urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

**Interpretation:** Vanillylmandelic acid and/or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monoamine oxidase-A deficiency.

**Reference Values:**
- <1 year: <35.0 mg/g creatinine
- 1 year: <30.0 mg/g creatinine
- 2-4 years: <25.0 mg/g creatinine
- 5-9 years: <15.0 mg/g creatinine
- 10-14 years: <9.0 mg/g creatinine
- > or =15 years (adults): <8.0 mg/g creatinine

**Clinical References:**

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**HBV 82551 Honeybee Venom, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to honeybee venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1359
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>2</td>
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<td>Strongly positive</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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</tbody>
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**HOP 82370**

**Hop Fruit, IgE, Serum**

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

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

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

**Reference Values:**

<table>
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<tr>
<th>Class</th>
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**Horse Dander, IgE, Serum**

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

Useful For: Establishing a diagnosis of an allergy to horse dander Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

Reference Values:

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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</tbody>
</table>

Reference values apply to all ages.


**Horsefly/ Stablefly, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to horsefly/stablefly Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

**Reference Values:**

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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
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Reference values apply to all ages.


**Horseradish (Armoracia rusticana/A.lapathifolia) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

**House Dust Mites/Dermatophagoides farinae, IgE, Serum**

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

**Useful For:** Establishing a diagnosis of an allergy to house dust mites/Dermatophagoides farinae
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode
-To confirm sensitization prior to beginning immunotherapy
-To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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

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**House Dust Mites/Dermatophagoides pteronyssinus, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to house dust mites/Dermatophagoides pteronyssinus
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode
-To confirm sensitization prior to beginning immunotherapy
-To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 1364
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House Dust Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cockroach, Dermatophagoides farinea, Dermatophagoides pteronyssinus, and house dust/H-S lab. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode. - To confirm sensitization prior to beginning immunotherapy. - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to house dust/Greer lab
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode
-To confirm sensitization prior to beginning immunotherapy
-To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson, MR
House Dust/H-S Lab, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to house dust/H-S lab Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>


HTLV I/II DNA, Qualitative Real-Time PCR

Reference Values: Reference Range: Not Detected

Human Anti-mouse Antibody (HAMA)

Reference Values: < or = 74 ng/mL
**Human Chorionic Gonadotropin (hCG) Immunostain, Technical Component Only**

**Clinical Information:** Human chorionic gonadotropin (hCG) is produced by the syncytiotrophoblasts of the placenta and has the same biologic properties as pituitary luteinizing hormone (LH). hCG stimulates androgen and progesterone production in women and helps maintain the corpus luteum of pregnancy. hCG is a heterodimeric hormone of 36kD with subunits designated alpha and beta. Many neoplasms including choriocarcinomas and adenocarcinomas may express hCG.

**Useful For:** Identification human chorionic gonadotropin expression in neoplasms

**Interpretation:** This test does not includes pathologist interpretation; only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Human Chorionic Gonadotropin (hCG), Quantitative, Pregnancy, Serum**

**Clinical Information:** Human chorionic gonadotropin (hCG) is a glycoprotein hormone that consists of 2 subunits (alpha and beta chains) that are associated to comprise the intact hormone. The alpha subunit is similar to those of luteinizing hormone, follicle-stimulating hormone, and thyrotropin (previously known as thyroid-stimulating hormone). The beta subunit of hCG differs from other pituitary glycoprotein hormones, which results in its unique biochemical and immunological properties. This method quantitates the sum of intact hCG plus the beta subunit. hCG is produced in the placenta during pregnancy. In nonpregnant individuals, it can also be produced by tumors of the trophoblast, germ cell tumors with trophoblastic components, and some non-trophoblastic tumors. The biological action of hCG serves to maintain the corpus luteum during pregnancy. It also influences steroid production. The serum in pregnant individuals contains mainly intact hCG. Measurement of the hCG concentration permits the diagnosis of pregnancy as early as 1 week after conception.

**Useful For:** Early detection of pregnancy Investigation of suspected ectopic pregnancy or other pregnancy-related complications Monitoring in vitro fertilization patients This test is not useful for detecting or monitoring tumors or gestational trophoblastic disease (GTD).

**Interpretation:** Values in pregnancy should double every 2 to 3 days for the first 6 weeks. Elevated concentrations of human chorionic gonadotropin (hCG) measured in the first trimester of pregnancy are observed in normal pregnancy but may serve as an indication of chorionic carcinoma, hydatiform mole, or multiple pregnancy. Decreasing hCG concentrations indicate threatened or missed abortion, recent termination of pregnancy, ectopic pregnancy, gestosis, or intrauterine death. Both normal and ectopic pregnancies generally yield positive results of pregnancy tests. The comparison of quantitative hCG measurements with the results of transvaginal ultrasonography (TVUS) may aid in the diagnosis of ectopic pregnancy. When an embryo is first large enough for the gestation sac to be visible on TVUS, the patient generally will have hCG concentrations between 1000 and 2000 IU/L. (These are literature values. Definitive values for this method have not been established at this time.) If the hCG value is this high and...
no sac is visible in the uterus, ectopic pregnancy is suggested. Elevated values will also be seen with choriocarcinoma and hydatiform mole. Peri- and postmenopausal females may have detectable hCG concentrations (< or = to 14 IU/L) due to pituitary production of hCG. Serum follicle-stimulating hormone measurement may aid in ruling-out pregnancy in this population. Cutoffs of greater than 20 to 45 IU/L have been suggested and are method dependent.

**Reference Values:**
Negative: <5 IU/L

**Clinical References:**

---

**Human Epididymis Protein 4, Serum**

**Clinical Information:** Human epididymis protein 4 (HE4) belongs to the family of whey acidic four-disulfide core (WFDC) proteins. Currently, the biologic function of HE4 is unknown. HE4 has been shown to be overexpressed in 93% of serous, 100% of endometrioid, and 50% of clear cell ovarian carcinomas. In a study of 233 patients with a pelvic mass, including 67 with epithelial ovarian cancer, HE4 had a higher sensitivity for ovarian cancer detection than cancer antigen 125 (CA 125), 72.9% versus 43.3%, respectively, at a specificity of 95%. Researchers also found HE4 to be elevated in more than half of the ovarian cancer patients who did not have elevated CA 125 levels; therefore, the combination of markers provided slightly improved cancer diagnostic sensitivity for the detection of ovarian cancer. The main established application of HE4 is in post-therapy monitoring of ovarian cancer patients, who had elevated pretreatment levels. In this setting, it complements CA 125 measurement and facilitates follow-up of patients with little or no CA 125 pretreatment elevations. Certain histological types of ovarian cancer (mucinous or germ cell tumors) rarely express HE4, therefore the use of HE4 is not recommended for monitoring of patients with these types of ovarian cancer.

**Useful For:** Aiding in monitoring patients with treated epithelial ovarian cancer for recurrence or progression This test should not be used as a screening test for ovarian cancer or for monitoring patients with mucinous or germ cell ovarian cancer.

**Interpretation:** Increase in human epididymis protein 4 (HE4) suggests recurrence or disease progression, while a decrease suggests therapeutic response. A change in serum HE4 concentration of greater than or equal to 20% is considered significant.

**Reference Values:**
Females: < or =140 pmol/L
Males: Not applicable

**Clinical References:**

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**Human Herpes Virus, Type 8 (HHV-8) Immunostain, Technical Component Only**

**Clinical Information:** Human herpes virus type 8 (HHV-8) infection can lead to the development of lymphoproliferative diseases or other neoplasms, especially in the setting of HIV. These neoplasms include the plasma cell variant of Castleman disease, Kaposi sarcoma, and primary effusion lymphoma.

**Useful For:** Identification of human herpes virus type 8 infection

**Interpretation:** This test does not include pathologist interpretation, only technical performance of
the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Human Herpesvirus 6 (HHV-6A and HHV-6B) by Quantitative PCR

Reference Values:
Not detected

The quantitative range of this assay is 3.0 – 6.0 log copies/mL (1,000 - 999,000 copies/mL).

A negative result (less than 3.0 log copies/mL or less than 1,000 copies/mL) does not rule out the presence of PCR inhibitors in the patient specimen or HHV6 DNA in concentrations below the level of detection of the test. Inhibition may also lead to underestimation of viral quantitation.

Human Herpesvirus-6, Molecular Detection, PCR, Plasma

Clinical Information: Herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These viruses contain DNA surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV] 1, HSV 2, varicella zoster virus [VZV], CMV, Epstein-Barr virus [EBV], HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections subsequent to latent association with cells.(1) Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. HHV-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the virus has been associated with central nervous system disease almost exclusively in immunocompromised patients.(1) HHV-6 is commonly detected in patients posttransplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, encephalitis, and bone marrow suppression. However, the majority of HHV-6 infections are asymptomatic.(2) The incidence of HHV-7 infection and its clinical manifestations posttransplantation are less well characterized. HHV-6 is designated as variant A (HHV-6A) or variant B (HH6-B) depending on restriction enzyme digestion patterns and on its reaction with monoclonal antibodies. Generally, variant B has been associated with exanthem subitum, whereas variant A has been found in many immunosuppressed patients.(3)

Useful For: As an adjunct in the rapid diagnosis of human herpesvirus-6 infection in plasma specimens

Interpretation: A positive result indicates the presence of specific DNA from human herpesvirus-6 (HHV-6) and supports the diagnosis of infection with this virus. A negative result indicates the absence of detectable DNA from HHV-6 in the specimen, but it does not negate the presence of the virus or active or recent disease.

Reference Values: Negative

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**Human Herpesvirus-6, Molecular Detection, PCR, Spinal Fluid**

**Clinical Information:** Human herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These viruses contain DNA surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV] 1, HSV 2, varicella zoster virus, CMV, Epstein-Barr virus, HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections subsequent to latent association with cells. Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. HHV-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the virus has been associated with central nervous system disease almost exclusively in immunocompromised patients. HHV-6 is commonly detected in patients posttransplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, encephalitis, and bone marrow suppression. However, the majority of HHV-6 infections are asymptomatic. The incidence of HHV-7 infection and its clinical manifestations posttransplantation are less well characterized. HHV-6 is designated as variant A (HHV-6A) or variant B (HH6-B) depending on restriction enzyme digestion patterns and on its reaction with monoclonal antibodies. Generally, variant B has been associated with exanthem subitum, whereas variant A has been found in many immunosuppressed patients.

**Useful For:** As an adjunct in the rapid diagnosis of human herpesvirus-6 infection in cerebrospinal fluid specimens

**Reference Values:**
Negative


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**Human Leukocyte Antigens (HLA) A-B-C Disease Association Typing Low Resolution, Blood**

**Clinical Information:** Human leukocyte antigens (HLA) are regulators of the immune response. HLA class I typing is used to identify HLA-matched platelets for alloimmunized refractory patients and identify presence of HLA antigens associated with a number of diseases or as drug hypersensitivity markers. Class I HLA antigens include A, B, and C loci. This assay is designed to provide low-to-medium resolution for HLA class I typing (A, B, C). Low-to-medium resolution defines the typing at the antigen level (first field). This is in contrast to high-resolution typing, which defines typing at the allele (molecular) level (second field or higher).

**Useful For:** Determining class I human leukocyte antigens (HLA) on specimens for those patients who have become refractory to platelet transfusions and identify potential disease association

**Interpretation:** Interpretation depends on the rationale for ordering the test.

**Reference Values:**
Not applicable
**Clinical References:**

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**Human Leukocyte Antigens (HLA)-DR-DQ Disease Association Typing Low Resolution, Blood**

**Clinical Information:** Human leukocyte antigen (HLA) class II genes (HLA-DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, -DPB1) are part of the major histocompatibility gene complex that encodes for proteins involved in immune recognition. This assay is designed to provide low-to-medium resolution for HLA class II typing. Low-to-medium resolution defines the typing at first field (antigen or allele group level). This is in contrast to high-resolution typing, which defines typing at second field or higher (allele level).

**Useful For:** Determining class II human leukocyte antigens (HLA) antigens to identify potential disease association and as markers for drug hypersensitivity.

**Interpretation:** Interpretation depends on the rationale for ordering the test.

**Reference Values:** Not applicable.

**Clinical References:**

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**Human Papillomavirus (HPV) DNA Detection with Genotyping, High Risk Types by PCR with Papanicolaou Smear Reflex, ThinPrep, Varies**

**Clinical Information:** Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in...
the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients who develop CIN, only a small percentage will progress to invasive cervical cancer. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18), as well as persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time), are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes types (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(1-3) In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction (PCR) has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1. Increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology 2. Reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US) Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% CI, 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for "other" HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV, but negative by routine cytology/Pap smear. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and/or 18 may have repeat cytology and HPV testing in 12 months.(1) Recently, the Food and Drug Administration (FDA) approved the use of the Roche cobas HPV test for primary screening of cervical and endocervical samples collected in ThinPrep/PreservCyt media. In addition, the age at which patients may be screened by the HPV test dropped from 30 to 25 years old.

**Useful For:** Screening for infection with high-risk (HR) human papillomavirus associated with the development of cervical cancer Individual genotyping of HPV-16 and/or HPV-18, if present This test is not recommended for evaluation of suspected sexual abuse. This test is not intended for women who have undergone hysterectomy. This test is not intended for use with samples other than those collected by a clinician using an endocervical brush or spatula and placed in the ThinPrep Pap test PreservCyt solution. This test is not intended for use in determining the need for treatment (ie, excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV16/18 positive should be monitored carefully for the development of high-grade cervical dysplasia according to current practice guidelines.

**Interpretation:** Human papillomavirus with genotyping polymerase chain reaction: A positive result
indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR)-HPV, consider referral for colposcopy, if clinically indicated. For women aged 25 years and older who are positive for HPV-16 and/or HPV-18, but negative by Pap smear, consider referral for colposcopy, if clinically indicated. Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Reference Values:**

Human papillomavirus (HPV) with Genotyping polymerase chain reaction (PCR): Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

ThinPrep Pap Test: Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

**Clinical References:**


**Human Papillomavirus (HPV) DNA Detection with Genotyping,**

**High-Risk Types by PCR, SurePath, Varies**

**Clinical Information:** Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV types can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients, only a small percentage will progress to invasive cervical cancer. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all...
women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18), as well as persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time), are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes types (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(1-3) In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% CI, 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for "other" HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV, but negative by routine cytology/Pap smear. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and/or 18 may have repeat cytology and HR HPV testing in 12 months.(1)

**Useful For:** Detection of high-risk (HR) genotypes associated with the development of cervical cancer An aid in triaging women with abnormal Pap smear results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present This test is not recommended for evaluation of suspected sexual abuse.

**Interpretation:** A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR HPV test in 12 months.

**Reference Values:** Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

Human Papillomavirus (HPV) DNA Detection with Genotyping, High-Risk Types by PCR, ThinPrep, Varies

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to “grade” CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients who develop CIN, only a small percentage will progress to invasive cervical cancer. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18), as well as persistent HPV infection (eg, an infection that is not cleared by the patient’s immune system over time), are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes types (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction (PCR) has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1. Increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology 2. Reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US) Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in
determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes, and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV-negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(1)

**Useful For:** Detection of high-risk (HR) genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can aid in triaging women with positive HR-HPV but negative Pap smear results This test is not recommended for evaluation of suspected sexual abuse. This test is not intended for use in determining the need for treatment (ie, excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV16/18 positive should be monitored carefully for the development of high-grade cervical dysplasia according to current practice guidelines. This test is not intended for women who have undergone hysterectomy. This test is not intended for use with samples other than those collected by a clinician using an endocervical brush or spatula and placed in the ThinPrep Pap test PreservCyt solution.

**Interpretation:** A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive-HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

**Reference Values:**
Negative for human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

**Clinical References:**
false-negative HPV DNA ISH result.

**Useful For:** Stratification of oropharyngeal squamous cell carcinoma

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Reference Values:**
Results are reported as positive or negative for types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82.

**Clinical References:**

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**HPVHL 70464 Human Papillomavirus (HPV) High/Low Risk, DNA In Situ Hybridization**

**Clinical Information:** Human papillomavirus (HPV) infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas. Persistent infections with high-risk genotypes (16, 18, 31, 33, and 51) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Reference Values:**
Results are reported as positive or negative for types 6 and 11 (low risk), and 16, 18, 31, 33, 51 (high risk).

**Clinical References:**

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**HPVLR 70465 Human Papillomavirus (HPV) Low Risk, DNA In Situ Hybridization**

**Clinical Information:** Human papillomavirus infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas.

**Useful For:** Detection of human papillomavirus (HPV) DNA from low-risk genotypes (6, 11)

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Reference Values:**
Results are reported as positive or negative for types 6 and 11.
**Clinical References:**


**HPVHR**

**Human Papillomavirus (HPV), High-Risk, DNA In Situ Hybridization**

**Clinical Information:** Persistent infections with high-risk human papillomavirus (HPV) genotypes (16, 18, 31, 33, and 51) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

**Useful For:** Detection of human papillomavirus DNA from high-risk genotypes (16, 18, 31, 33, and 51)

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Clinical References:**


**FHPL**

**Human Placental Lactogen (HPL)**

**Reference Values:**

- Males and nonpregnant Woman: 0.00 - 0.10 mcg/mL
- 1st Trimester of Pregnancy: 0.20 - 2.10 mcg/mL
- 2nd Trimester of Pregnancy: 0.50 - 6.70 mcg/mL
- 3rd Trimester of Pregnancy: 4.50 - 12.80 mcg/mL

**HPL**

**Human Placental Lactogen Immunostain, Technical Component Only**

**Clinical Information:** Human placental lactogen (HPL) is a hormone secreted by the placenta during normal pregnancy. Detection of this hormone may help in diagnosis of placenta-related tumors such as trophoblastic tumors and choriocarcinomas.

**Useful For:** Aids in the identification of placenta-related tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Human T-Cell Lymphotropic Virus Types 1 and 2 (HTLV-1/-2) Antibody Confirmation, Spinal Fluid

**Clinical Information:** Human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) are closely related exogenous human retroviruses. HTLV-1 was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-2 was identified from a patient with hairy cell leukemia in 1982. HTLV-1 infection is endemic in southwestern Japan, Caribbean basin, Melanesia, and parts of Africa, where HTLV-1 seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-1 and HTLV-2 seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-1, with most of them reporting a history of birth in HTLV-1-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-1 occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-1 infection: adult T-cell leukemia or lymphoma (ATL) and a chronic degenerative neurologic disease known as HTLV-1-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis have also been reported in HTLV-1-infected patients. HTLV-2 is prevalent among injection drug users in the United States and in Europe, and more than 80% of HTLV infections in drug users in the United States are due to HTLV-2. HTLV-2 also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-2-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-2 is transmitted similarly to HTLV-1, but much less is known about the specific modes and efficiency of transmission of HTLV-2. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-2 infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-2 has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as enzyme immunoassay. For accurate diagnosis of HTLV-1 or HTLV-2 infection, all initial screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

**Useful For:** Confirmatory detection of human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2)-specific IgG antibodies in spinal fluid specimens that are consistently reactive by initial screening tests Differentiating between HTLV-1- and HTLV-2-specific IgG antibodies present in spinal fluid

**Interpretation:** Negative confirmatory test results indicate the absence of both human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2)-specific IgG antibodies in spinal fluid and a low probability of an HTLV-1/-2-associated neurologic disorder. A reactive screening (enzyme immunoassay) result with a negative or indeterminate confirmatory (line immunoassay) test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing with a new specimen can clarify the final infection status. Persistently indeterminate confirmatory test results indicate an absence of HTLV infection. Positive results for HTLV-1 antibodies indicate the confirmed presence of HTLV-1 IgG antibodies in spinal fluid, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-I and p19-I band intensity is greater than the gp46-II band intensity. Positive results for HTLV-2 antibodies indicate the confirmed presence of HTLV-2 IgG antibodies in spinal fluid, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-II band intensity is a) greater than the gp46-I band intensity and b) equal or greater than the sum of the gp46-I and p19-I band intensity. Indeterminate results indicate the presence of the gp21-I/-II band only or combination of any 2 bands without a detectable gp21-I/-II band. Patients with indeterminate test results with known risk factors for HTLV-1 or HTLV-2 infection should undergo
repeat confirmatory antibody testing with a new specimen to determine final infection status. Differentiation of HTLV-1 and HTLV-2 infection is not possible (ie, nontypeable HTLV antibodies) when the band intensity pattern does not meet the criteria of positive HTLV-1 or HTLV-2 antibody band intensity pattern. Unreadable results indicate the presence of nonspecific background reactivity that is inhibiting the visualization of specific bands on the test strip. Repeat testing with a new specimen is recommended. Invalid results indicate that nonspecific band reactivity is present. Submit another specimen for retesting, if clinically indicated.

Reference Values:
Negative


Human T-Cell Lymphotropic Virus Types 1 and 2 (HTLV-1/-2) Antibody Screen with Confirmation, Spinal Fluid

Clinical Information: Human T-cell lymphotropic virus types 1 and 2 (HTLV-1/-2) are closely related exogenous human retroviruses. HTLV-1 was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-2 was identified from a patient with hairy cell leukemia in 1982. HTLV-1 infection is endemic in southwestern Japan, the Caribbean basin, Melanesia, and parts of Africa, where HTLV-1 seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-1 and HTLV-2 seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-1, with most of them reporting a history of birth in HTLV-1-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-1 occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-1 infection: adult T-cell leukemia or lymphoma, and a chronic degenerative neurologic disease known as HTLV-1-associated myelopathy or tropical spastic paraparesis. Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis also have been reported in HTLV-1-infected patients. HTLV-2 is prevalent among injection drug users in the United States and in Europe, with more than 80% of HTLV infections in drug users in the United States due to HTLV-2. HTLV-2 also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-2-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-2 infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-2 has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as enzyme immunoassay (EIA). For accurate diagnosis of HTLV-1 or HTLV-2 infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Qualitative screening detection of human T-cell lymphotropic virus types 1 and 2 (HTLV-1/-2) specific antibodies with confirmation and differentiation between HTLV-1 and HTLV-2 infection
**Interpretation:** Negative screening results indicate the absence of both human T-cell lymphotropic virus types 1 and 2 (HTLV-1/-2)-specific IgG antibodies in spinal fluid. A reactive screening test result is suggestive of infection with either HTLV-1 or HTLV-2. However, this result does not confirm infection (eg, low specificity), and it cannot differentiate between HTLV-1 and HTLV-2 infection. Specimens with reactive screening test results will be tested automatically by the line immunoassay (LIA) confirmatory test. Positive LIA results provide confirmatory evidence of infection with HTLV-1 or HTLV-2. A reactive screening result with a negative or indeterminate confirmatory test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection.

**Reference Values:**

Negative

**Clinical References:**

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**Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/-II) Antibody Confirmation, Serum**

**Clinical Information:** Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. HTLV-I infection is endemic in southwestern Japan, the Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I infection: adult T-cell leukemia or lymphoma (ATL) and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis have also been reported in HTLV-I-infected patients. HTLV-II is prevalent among injection drug users in the United States and in Europe, and more than 80% of HTLV infections in drug users in the United States are due to HTLV-II. HTLV-II also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as enzyme immunoassay. For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

**Useful For:** Confirmatory detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in human serum specimens that are consistently reactive by initial
Interpretation: Negative confirmatory test results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in serum. A reactive screening (enzyme immunoassay) result with a negative or indeterminate confirmatory (line immunoassay) test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing with a new specimen can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection. Positive results for HTLV-I antibodies indicate the confirmed presence of HTLV-I IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-I and p19-I band intensity is greater than the gp46-II band intensity. Positive results for HTLV-II antibodies indicate the confirmed presence of HTLV-II IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the gp46-II band intensity is a) greater than the gp46-I band intensity and b) equal or greater than the sum of the gp46-I and p19-I band intensity. Indeterminate results indicate the presence of gp21-I/-II band only or combination of any 2 bands without a detectable gp21-I/-II band. Patients with indeterminate test results with known risk factors for HTLV-I or HTLV-II infection should undergo repeat confirmatory antibody testing with a new specimen to determine final infection status. Differentiation of HTLV-I and HTLV-II infection is not possible (ie, nontypeable HTLV antibodies) when the band intensity pattern does not meet the criteria of positive HTLV-I or HTLV-II antibody band intensity pattern. Unreadable results indicate the presence of nonspecific background reactivity that is inhibiting the visualization of specific bands on the test strip. Repeat testing with a new specimen is recommended. Invalid results indicate that nonspecific band reactivity is present. Submit another serum specimen for retesting, if clinically indicated.

Reference Values:
Negative

Clinical References:
endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as enzyme immunoassay (EIA). For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

**Useful For:** Qualitative detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific antibodies with confirmation and differentiation between HTLV-I and HTLV-II infection. This test is not intended for screening blood, human cells, tissues, or solid-organ donors. This test is not intended for use on cord blood specimens.

**Interpretation:** Negative screening results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I- and HTLV-II)-specific IgG antibodies in serum. A reactive screening test result is suggestive of infection with either HTLV-I or HTLV-II. However, this result does not confirm infection (eg, low specificity), and it cannot differentiate between HTLV-I and HTLV-II infection. Specimens with reactive screening test results will be tested automatically by the line immunoassay (LIA) confirmatory test. Positive LIA results provide confirmatory evidence of infection with HTLV-I or HTLV-II. A reactive screening result with a negative or indeterminate confirmatory test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection.

**Reference Values:**
Negative


**MPS2Z 35463 Hunter Syndrome, Full Gene Analysis, Varies**

**Clinical Information:** Mucopolysaccharidosis type II (MPS-II), also known as Hunter syndrome, is a rare X-linked condition caused by variants in the IDS gene. MPS-II is characterized by reduced or absent activity of the iduronate 2-sulfatase enzyme. The clinical features and severity of symptoms of MPS-II are widely variable, ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, joint contractures, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. Female carriers are usually asymptomatic. The IDS gene is located on the X chromosome and has 9 exons and is the only known gene to be associated with MPS-II. The recommended first-tier test for mucopolysaccharidosis type II is biochemical testing that measures iduronate 2-sulfatase enzyme activity in blood: I2SW / Iduronate-2-Sulfatase, Whole Blood or blood spots: I2SBS / Iduronate-2-Sulfatase, Blood Spot. Individuals with decreased or absent enzyme activity are more likely to have a variant in the IDS gene identifiable by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers. Additionally, measurement of mucopolysaccharides in blood can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot).
**Useful For:** Confirmation of a diagnosis of mucopolysaccharidosis type II (Hunter syndrome) Carrier testing when there is a family history of mucopolysaccharidosis type II (Hunter syndrome), but disease-causing variants have not been previously identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Huntington Disease, Molecular Analysis, Varies**

**Clinical Information:** Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder caused by a CAG repeat expansion in the HTT gene. HD is associated with cognitive impairment leading to dementia and a wide range of neuropsychiatric problems including apathy, depression, anxiety, and other behavioral disturbances. Additionally, affected individuals typically develop extrapyramidal symptoms (e.g., dystonia, dysarthria, chorea, gait disturbance, postural instability, oculomotor dysfunction).

**Useful For:** Molecular confirmation of clinically suspected cases of Huntington disease (HD)
Presymptomatic testing for individuals with a family history of HD and a documented expansion in the HTT gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles: <27 CAG repeats
Intermediate alleles: 27-35 CAG repeats
Reduced penetrance: 36-39 CAG repeats
Full penetrance: >39 CAG repeats
An interpretive report will be provided.

**Clinical References:**

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**Hurler Syndrome, Full Gene Analysis, Varies**

**Clinical Information:** Mucopolysaccharidosis type I (MPS-I) can be categorized into 3 syndromes, Hurler syndrome, Scheie syndrome, and Hurler-Scheie syndrome. MPS-I, inherited in an autosomal recessive manner, is caused by variants in the IDUA gene. Furthermore, MPS-I is characterized by reduced or absent activity of the alpha-L-iduronidase enzyme. Hurler syndrome (severe MPS-I) has early onset and consists of skeletal deformities, coarse facial features, corneal clouding, hepatosplenomegaly, cardiac involvement, hearing loss, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. Hurler-Scheie syndrome and Scheie syndrome (attenuated MPS-I) have onset between 3 to 10 years of age.
age and consist of corneal clouding, cardiac involvement, moderate-to-severe hearing loss, and progressive pulmonary disease. Typically skeletal and joint involvement is the most significant source of discomfort for attenuated MPS-I. Intellect with attenuated MPS-I is typically normal or nearly normal. The IDUA gene is located on chromosome 4 and has 14 exons. IDUA is the only known gene to be associated with MPS-I, and the 3 syndromes appear to be caused by different combinations of variants. The recommended first-tier test for MPS-I is biochemical testing that measures alpha-L-iduronidase enzyme activity in blood: IDUA/W Alpha-L-Iduronidase, Leukocytes or PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot. Individuals with decreased or absent enzyme activity are more likely to have 2 identifiable variants in the IDUA gene by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers. Additionally, measurement of mucopolysaccharides in blood can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot).

Useful For: Identifying variants within the IDUA gene Confirmation of a diagnosis of mucopolysaccharidosis type I (MPS-I) Carrier testing when there is a family history of MPS-I, but disease-causing variants have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Hydrocodone and metabolites

Reference Values:
Reference Range:

Hydrocodone, unconjugated: 10-100 ng/mL

Hydromorphone, unconjugated: 1-30 ng/mL

Dihydrocodeine, unconjugated: Not established ng/mL

Hydrocodone with Metabolite Confirmation, Random, Urine

Clinical Information: Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxy metabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days.
prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. The detection interval for the opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of hydrocodone, norhydrocodone, and hydromorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**
Negative
Cutoff concentrations:
- Hydrocodone-by LC-MS/MS: 25 ng/mL
- Norhydrocodone-by LC-MS/MS: 25 ng/mL
- Hydromorphone-by LC-MS/MS: 25 ng/mL

**Clinical References:**

**HYDMU 62615**

**Hydromorphone Confirmation, Random, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (e.g., codeine, hydrocodone, hydromorphone, oxycodone). Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone.

**Useful For:** Detection and quantification of hydromorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**
Negative
Cutoff concentrations:
- Hydromorphone-by LC-MS/MS: 25 ng/mL

**Clinical References:**
**Hydroxychloroquine, Serum**

**Clinical Information:** Hydroxychloroquine is an antimalarial drug used to treat or prevent malaria. It is highly effective against erythrocytic forms of Plasmodium, but not effective against exoerythrocytic forms of parasites. Hydroxychloroquine is also used to treat symptoms of acute or chronic rheumatoid arthritis and systemic lupus erythematosus (SLE). Adult doses range from 400 mg/week for suppressive therapy to 1200 mg/day for acute malaria attacks. Typical daily doses of 200 to 600 mg are used for SLE and rheumatoid diseases. Hydroxychloroquine has a long terminal elimination half-life in blood (>40 days), which exceed those in plasma. The oral bioavailability averages 75%. Hydroxychloroquine accumulates in several organs, especially melanin-containing retina and skin. Mild to moderate overdose can result in gastrointestinal effects (ie, nausea, vomiting, and abdominal pain), headache, visual and hearing disturbances, and neuromuscular excitability. Acute hepatitis, cardiotoxicity, and retinopathy may occur with therapeutic doses. The effects of overdosage with hydroxychloroquine include headache, drowsiness, visual disturbances, convulsions, cardiovascular collapse, and respiratory arrest. Toxic retinopathy has also been associated with higher doses and longer duration of use.

**Useful For:** Monitoring serum hydroxychloroquine concentrations, assessing compliance, and adjusting dosage in patients

**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response, noncompliance, or adverse effects. Concentrations less than 106 ng/mL have been associated with non-compliance.

**Reference Values:** For suppressive treatment of malaria, suggested plasma or serum concentrations should be >10 ng/mL.

For systemic lupus erythematosus, proposed serum target concentrations should be > or =500 ng/mL.

**Clinical References:**
**Clinical Information:** Acylcarnitine analysis is included in newborn screening blood tests and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxyglutaric acid (2OH-GA), 3-hydroxyglutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by liquid chromatography-tandem mass spectrometry allows better differentiation among C4-acylcarnitine and glutarylcarnitine/C10-OH isomers. C4-acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short-chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive. There is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics and Genomics (ACMG) Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) using dried blood spot specimens Evaluation of patients with abnormal newborn screens showing elevations of C4-acylcarnitine to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aiding in diagnosis of glutaric acidemia type 2

**Interpretation:** Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short-chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type I (GA1). Elevation of GA, 2-hydroxyglutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type II (GA2).

**Reference Values:**
- 2-OH Glutaric acid: < or =25 nmol/mL
- 3-OH Glutaric acid: < or =1.5 nmol/mL
- Glutaric acid: < or =1.5 nmol/mL
- Methylsuccinic acid: < or =0.45 nmol/mL
- Ethylmalonic acid: < or =3.5 nmol/mL

**Clinical References:** 1. Rinaldo P, Cowan TM, Matern D: Acylcarnitine profile analysis. Genet
Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid, and Methylsuccinic Acid, Plasma

Clinical Information: Acylcarnitine analysis is included in newborn screening blood tests and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxyglutaric acid (2OH-GA), 3-hydroxyglutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by liquid chromatography-tandem mass spectrometry allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers. C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive. There is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics and Genomics (ACMG) Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) using plasma specimens Evaluation of patients with abnormal newborn screens
showing elevations of C4- acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aiding in diagnosis of glutaric acidemia type 2

**Interpretation:** Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type I (GA1). Elevation of GA, 2-hydroxyglutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type II (GA2).

**Reference Values:**
- 2-OH Glutaric acid < or =4.5 nmol/mL
- 3-OH Glutaric acid < or =0.7 nmol/mL
- Glutaric acid < or =0.8 nmol/mL
- Methylsuccinic acid < or =0.3 nmol/mL
- Ethylmalonic acid < or =1.5 nmol/mL

**Clinical References:**
levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutaryl carnitine (C5-DC) is elevated in glutaric academia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 is caused by a deficiency of glutaryl-CoA dehydrogenase. GA1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors." Glutaric academia type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood, and muscle weakness in childhood and adulthood. In addition to elevations in GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics and Genomics (ACMG) Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

**Useful For:**
- Evaluation of patients with an abnormal newborn screen showing elevations of glutaryl carnitine (C5-DC) using serum specimens Evaluation of patients with abnormal newborn screens showing elevations of C4-acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies
- Diagnosis of glutaric academia type 1
- Aiding in diagnosis of glutaric academia type 2

**Interpretation:** Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl-CoA dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric academia type I (GA1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric academia type II (GA2).

**Reference Values:**
- 2-OH Glutaric acid < or =4.5 nmol/mL
- 3-OH Glutaric acid < or =0.7 nmol/mL
- Glutaric acid < or =0.8 nmol/mL
- Methylsuccinic acid < or =0.3 nmol/mL
- Ethylmalonic acid < or =1.5 nmol/mL

**Clinical References:**
Hydroxyzine (Vistaril, Atarax), Serum

Reference Values:
Reference Range: 10 - 100 ng/mL

Hyperoxaluria Panel, Random, Urine

Clinical Information: Increased urinary oxalate frequently leads to renal stone formation and renal insufficiency. Identifying the cause of hyperoxaluria has important implications in therapy, management and prognosis. Hyperoxalurias are classified as primary and secondary. Primary hyperoxaluria is an inherited disorder of oxalate metabolism while secondary hyperoxaluria is an acquired condition resulting from either increased intake of dietary oxalate or altered intestinal oxalate absorption. Primary hyperoxalurias are classified into types 1, 2, and 3. Hyperoxaluria type 1 (PH1) is an autosomal recessive disorder resulting in a deficiency of peroxisomal alanine: glyoxylate aminotransferase due to variants in the AGXT gene. It is characterized by increased urinary oxalic, glyoxylic, and glycolic acids. PH1 is the most common type with manifestations that include deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and end-stage renal disease. Calcium oxalate deposits can be further deposited in other tissues such as the heart and eyes, and lead to a variety of additional symptoms. Age of onset is variable with a small percentage of patients presenting in the first year of life with failure to thrive, nephrocalcinosis, and metabolic acidosis. Approximately half of affected individuals show manifestations of PH1 in late childhood or early adolescence, and the remainder present in adulthood with recurrent renal stones. Some individuals with PH1 respond to supplemental pyridoxine therapy. Hyperoxaluria type 2 (PH 2) is due to a defect in GRHPR gene resulting in a deficiency of the enzyme hydroxypropanoyl-CoA reductase. PH2 is inherited in an autosomal recessive manner and is identified by an increase in urinary oxalic and glyceric acids. Like PH1, PH2 is characterized by deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and end-stage renal disease. Most individuals have symptoms of PH2 during childhood, and it is thought that PH2 is less common than PH1. Hyperoxaluria type 3 (PH3), due to recessive variants in HOGA1 (formerly DHDPSL), occurs in a small percentage of individuals with primary hyperoxaluria. HOGA1 encodes a mitochondrial 4-hydroxy-2-oxoglutarate aldolase that catalyzes the 4th step in the hydroxyproline pathway. PH3 is characterized biochemically by increased urinary excretion of oxalate and 4-hydroxy-2-oxoglutarate (HOG). As with PH types 1 and 2, PH type 3 is characterized by calcium-oxalate deposition in the kidneys or kidney stone formation. Most individuals with PH3 have early onset disease with recurrent kidney stones and urinary tract infections as common symptoms. End-stage renal disease is not a characteristic of PH3. Of note, individuals with heterozygous variants in HOGA1 can have variable and intermittent elevations of urine oxalate. Secondary hyperoxalurias are due to hyperabsorption of oxalate (enteric hyperoxaluria); total parenteral nutrition in premature infants; ingestion of oxalate, ascorbic acid, or ethylene glycol; or pyridoxine deficiency, and may respond to appropriate therapy. A diagnostic workup in an individual with hyperoxaluria demonstrates increased concentration of oxalate in urinary metabolite screening. If glycolate, glycerate, or HOG is present, a primary hyperoxaluria is indicated. Additional analyses can include molecular testing for PH1 (AGXTZ / AGXT Gene, Full Gene Analysis, Varies), PH2 (GRHPZ / GRHPR Gene, Full Gene Analysis, Varies), or PH3 (HOGA1 sequencing).

Useful For: Distinguishing between primary and secondary hyperoxaluria Distinguishing between primary hyperoxaluria types 1, 2, and 3

Interpretation: Increased concentrations of oxalate and glycolate indicate type 1 hyperoxaluria. Increased concentrations of oxalate and glycerate indicate type 2 hyperoxaluria. Increased concentrations of oxalate and 4-hydroxy-2-oxoglutarate indicate type 3 hyperoxaluria. Increased concentrations of oxalate with normal concentrations of glycolate, glycerate, and 4-hydroxy-2-oxoglutarate indicate secondary hyperoxaluria.

Reference Values:
GLYCOLATE
< or =17 years: < or =75 mg/g creatinine
> or =18 years: < or =50 mg/g creatinine
GLYCERATE  
< or =31 days: < or =75 mg/g creatinine
32 days - 4 years: < or =125 mg/g creatinine
5 - 10 years: < or =55 mg/g creatinine
> or =11 years: < or =25 mg/g creatinine

OXALATE  
< or =6 months: < or =400 mg/g creatinine
7 months - 1 year: < or =300 mg/g creatinine
2 - 6 years: < or =150 mg/g creatinine
7 - 10 years: < or =100 mg/g creatinine
> or =11 years: < or =75 mg/g creatinine

4-HYDROXY-2-OXOGLUTARATE (HOG)  
< or =10 mg/g creatinine

Clinical References:  

FAVI 91509  
Hypersensitivity Pneumonitis Avian Panel  
Clinical Information: A hypersensitivity pneumonitis (HP) due to the inhalation and sensitization to avian antigens. Immunodiffusion is used to evaluate the presence of precipitating antibodies in the sera of patients with HP due to the sensitization to various species of birds.  
Reference Values: This panel includes the following antigens:

- Pigeon Sera
- Pigeon DE
- Cockatiel
- Parakeet
- Parrot

This result must be correlated with patient's clinical response and should not solely be considered in the diagnosis.

FHPP2 57595  
Hypersensitivity Pneumonitis FEIA Panel II  
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200  
Reference Values:

- Alternaria tenuis/alternata IgG <12 mcg/mL
- Aspergillus fumigatus IgG <46 mcg/mL
- Aureobasidium pullulans IgG <18 mcg/mL
- Micropolyspora faeni IgG <5 mcg/mL
- Penicillium Chrysogenum/notatum IgG <22 mcg/mL
Phoma betae IgG  <8 mcg/mL
Thermoactinomyces vulgaris IgG  <13 mcg/mL
Trichoderma viride IgG  <10 mcg/mL

Antibody levels greater than the reference range indicate that the patient has been immunologically sensitized to the antigen. The significance of elevated IgG depends on the nature of the antigen and the patient's clinical history. The test method was the Phadia ImmunoCAP.

**HYPs**

**Hypersensitivity Pneumonitis Panel, IgG, Serum**

**Clinical Information:** Hypersensitivity pneumonitis (HP) is a heterogeneous disease caused by exposure to organic dust antigens, animal proteins, chemicals, medications, or microorganisms (eg, Thermoactinomyces vulgaris, Micropolyspora faeni, Aspergillus fumigatus). The immunopathogenesis of disease is not known; but, several immunologic mechanisms may play a role in producing alveolitis, including cellular immunity mediated by CD4 and CD8 T lymphocytes, immune-complex mediated inflammation, complement activation, or activation of alveolar macrophages.(1) HP is suspected clinically in patients who present with intermittent or progressive pulmonary symptoms and interstitial lung disease. The diagnosis is established by compatible clinical and radiographic findings, pulmonary function tests, and demonstration of specific antibodies to organic antigens known to cause the disease.

**Useful For:** Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni

**Interpretation:** Elevated concentrations of IgG antibodies to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to one or more of these organic antigens.

**Reference Values:**
Aspergillus fumigatus, IgG ANTIBODIES
- <4 years: not established
- > or =4 years: < or =102 mg/L
Micropolyspora faeni, IgG ANTIBODIES
- 0-12 years: < or =4.9 mg/L
- 13-18 years: < or =9.1 mg/L
- >18 years: < or =13.2 mg/L

Thermoactinomyces vulgaris, IgG ANTIBODIES
- 0-12 years: < or =6.6 mg/L
- 13-18 years: < or =11.0 mg/L
- >18 years: < or =23.9 mg/L


**HCMGP**

**Hypertrophic Cardiomyopathy Multi-Gene Panel, Blood**

**Clinical Information:** The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left...
ventricular noncompaction (LVNC). The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The pathological hallmark of HCM is "myocyte disarray" where there is a loss of parallel alignment of myocytes in the heart wall. HCM is most often caused by genes encoding the cardiac sarcomere, the functional contractile unit of the heart muscle. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can cause life-threatening arrhythmias, which increase the risk of sudden cardiac death. The incidence of HCM in the general population is approximately 1 in 500. Inheritance is autosomal dominant, but compound heterozygosity (biallelic variants in the same gene) and digenic inheritance (variants in 2 different HCM-associated genes) do occur. The MYBPC3, MYL2, MYL3, MYH7, ACTC, TPM1, TNN13, TNN2, and CAV3 genes are involved in formation and regulation of the cardiac sarcomere, and account for the majority of variants in HCM. Left ventricular hypertrophy can also be caused by metabolic or storage disorders such as Fabry disease (GLA gene), Danon disease (LAMP2 gene), and Wolf-Parkinson-White syndrome associated with variants in the PRKAG2 gene. The TTR gene causes familial transthyretin amyloidosis, which is characterized by buildup of amyloid protein that affects the peripheral and autonomic nervous system. Other nonneuropathic changes may also be involved, including cardiomyopathy. See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Hypertrophic Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKRD1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tayekeyata-type distal myopathy, rippling muscle disease CSR3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD GLA Galactosidase, alpha X-linked Fabry disease LAMP2 Lysosome-associated membrane protein 2 X-linked Danon disease MYBP3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light chain 2, regulatory, cardiac, slow AD HCM MYL3 Myosin, light chain 3, alkali, ventricular, skeletal, slow AD, AR HCM MYLK2 Myosin light chain kinase 2 AD HCM MYOZ2 Myozenin 2 AD HCM, DCM, LQTS, LGMD, Titin-cap (telethonin) AD, AR HCM, DCM, LGMD TNNC1 Troponin C, slow AD HCM, DCM, TNN3 Troponin I, cardiac AD, AR DCM, HCM, RCM TNN2 Troponin T2, cardiac AD HCM, DCM, RCM, LVNC TPM1 Troponycin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, myopathy TTR Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Congenital heart defects (CHD), long QT syndrome (LQTS), limb-girdle muscular dystrophy (LGMD), autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hypertrophic cardiomyopathy (HCM) Establishing a diagnosis of a hereditary HCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.

HYPOG 82439

Hypoglycemic Agent Screen, Serum

**Clinical Information:** The metabolic and hormonal profiles of insulinoma and sulfonylurea-induced hypoglycemia are identical. Therefore, in the evaluation of the hypoglycemic patient, the possible use of oral hypoglycemic agents as the cause for low blood glucose and elevated plasma insulin must be considered. Absence of hypoglycemic drugs in blood serum during an episode of low blood glucose should be demonstrated before considering pancreatic exploration for suspected insulinoma.

**Useful For:** Evaluation of suspected insulinoma characterized by hypoglycemia and increased plasma insulin concentration. Detecting drugs that stimulate insulin secretion. If hypoglycemia is the result of one of these drugs, the test will detect the drug at physiologically significant concentrations in serum during an episode of hypoglycemia. Drugs detected by this procedure are:
- The first-generation sulfonylureas—acetohexamide, chlorpropamide, tolazamide, and tolbutamide
- The second-generation sulfonylureas—glimepiride, glipizide, and glyburide
- The meglitinide—repaglinide

Drugs designed to make tissues more sensitive to insulin that do not induce hypoglycemia, such as pioglitazone, rosiglitazone, and troglitazone (recently withdrawn from the United States market) are not included in this screen test. Drugs that lower blood glucose through mechanisms not related to stimulation of insulin secretion, such as acarbose, metformin, and miglitol are not included in this screen test.

**Interpretation:** Use of hypoglycemic agents outside of the context of treatment of type 2 diabetes is likely to cause hypoglycemia associated with elevated plasma insulin. Patients presenting with hypoglycemia due to ingestion of a first-, second-, or third-generation hypoglycemic agent will have drug present in serum greater than the minimum effective concentration (see Reference Values). Presence of drug indicates that the patient has recently ingested a hypoglycemic agent.

**Reference Values:**

**ACETOHEXAMIDE**
Negative: <1,000 ng/mL

**CHLORPROPAMIDE**
Negative: <1,000 ng/mL

**TOLAZAMIDE**
Negative: <20 ng/mL

**TOLBUTAMIDE**
Negative: <50 ng/mL

**GLIMEPIRIDE**
Negative: <20 ng/mL
GLIPIZIDE
Negative: <3 ng/mL

GLYBURIDE
Negative: <3 ng/mL

REPAGLINIDE
Negative: <3 ng/mL

Note: The report indicates a specific drug is positive if that drug is detected at a concentration greater than the sensitivity limit. The test sensitivity limit listed for each drug is lower than the concentration that will cause increased insulin and decreased glucose.


HIF2A
Hypoxia-Inducible Factor Alpha (EPAS1/HIF2A) Gene, Exons 9 and 12 Sequencing, Whole Blood

Clinical Information: Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by variants in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new alterations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF2A/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF2A, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal level to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Genetic alterations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in...
erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and, are mainly missense or small deletion and insertions resulting in stop codons, and are heterozygous truncating variants. EPOR variants are associated with decreased to normal EPO levels and normal p50 values (see Table).

**Useful For:** Assessing HIF2A/EPAS1 in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** An interpretive report will be provided as a part of HEMP / Hereditary Erythrocytosis Mutations, Whole Blood and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

An interpretive report will be provided.

**Clinical References:**
8. 2012:22-723

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**FIBUP**

**57703**

**Ibuprofen (Motrin, Advil, Nuprin), serum**

**Reference Values:**
Reference Range: 10.0 - 50.0 ug/mL

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**ICOSI**

**113518**

**ICOS (CD278), Immunostain, Technical Component Only**

**Clinical Information:** ICOS (inducible T-cell costimulator or CD278: cluster of differentiation 278) is primarily expressed on activated CD4+ and CD8+ T cells where it regulates immune responses and plays a role in the regulation of T-follicular helper cells. ICOS is a sensitive marker for identifying T-cell lymphomas of follicular helper T-cell origin, especially certain patterns of angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphomas with T-follicular helper phenotype (PTCL-TFH).

**Useful For:** Classification of T-cell lymphomas
**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**LCHB**

**Id, Histoplasma/Blastomyces PCR (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**RMALD**

**Ident by MALDI-TOF Mass Spec (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**LCCI**

**Ident Rapid PCR Coccidioides (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**PCRID**

**Identification by PCR (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**LCCA**

**Identification, Candida auris, Rapid PCR (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**COMM**

**Identification, Commercial Kit (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**LCTB 610320**

**Identification, Mycobacterium tuberculosis Complex, Rapid PCR (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**ISNGS 609732**

**Identification, Next-Generation Sequencing (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**IDH1 70468**

**IDH1 Mutation (R132H) Immunostain, Technical Component Only**

**Clinical Information:** Antihuman isocitrate dehydrogenase 1 (IDH1) R132H antibody binds to IDH1-mutated protein but does not bind the wild-type IDH1 protein. IDH1 R132H point mutations are frequently seen in World Health Organization grade II and III gliomas and are believed to constitute an early step in tumorigenesis. IDH1 R132H can be used as a diagnostic marker to help differentiate infiltrating gliomas from glial and as a prognostic marker for gliomas and secondary glioblastoma multiforme. IDH1 R132H antibody shows strong cytoplasmic staining and weaker nuclear staining in tumor cells with the R132H-mutated peptide. Diffuse staining of the fibrillary tumor matrix is also seen.

**Useful For:** Classification of gliomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**I2SW 61902**

**Iduronate-2-Sulfatase, Blood**

**Clinical Information:** The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate, also known as glycosaminoglycans (GAG). Accumulation of GAG in the lysosomes interferes with normal functioning of cells, tissues, and organs. Mucopolysaccharidosis II (MPS II, Hunter syndrome) is an X-linked lysosomal storage disorder caused by the deficiency of iduronate sulfatase (IDS) enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints,
cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment availability, including hematopoietic stem cell transplantation and enzyme replacement therapy, makes early diagnosis desirable, as early initiation of treatment has been shown to improve clinical outcomes. Newborn screening for MPS II has been implemented in some states. A diagnostic workup in an individual with MPS II typically demonstrates elevated levels of urinary GAG and increased amounts of both dermatan sulfate and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine and MPSBS / Mucopolysaccharides, Blood Spot). Reduced or absent activity of IDS can confirm a diagnosis of MPS II but may also be deficient in individuals with multiple sulfatase deficiency. Enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing variant in affected individuals and subsequent carrier detection in female relatives (see MPS2Z / Hunter Syndrome, Full Gene Analysis, Varies). Currently, no clear genotype-phenotype correlations have been established.(1)

**Useful For:** Diagnosis of mucopolysaccharidosis II (MPS II, Hunter syndrome) in whole blood specimens This test is not useful for determining carrier status for MPS II.

**Interpretation:** Specimens with results below 1.5 nmol/hour/mL in properly submitted specimens are consistent with iduronate-2-sulfatase deficiency (mucopolysaccharidosis II: MPS II). If clinically indicated, consider further confirmation by molecular genetic analysis of the IDS gene. Note that this enzyme's activity can also be reduced in multiple sulfatase deficiency (MSD).(2) If clinically indicated, consider biochemical genetic testing of other sulfatases or molecular genetic testing of the SUMF1 gene to exclude MSD. Normal results (≥1.5 nmol/hour/mL) are not consistent with iduronate-2-sulfatase deficiency.

**Reference Values:**

> or =1.5 nmol/hour/mL

**Clinical References:**

initiation of treatment has been shown to improve clinical outcomes. Newborn screening for MPS II has been implemented in some states. A diagnostic workup in an individual with MPS II typically demonstrates elevated levels of urinary glycosaminoglycans and increased amounts of both dermatan and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine and MPSBS / Mucopolysaccharides, Blood Spot). Reduced or absent activity of IDS can confirm a diagnosis of MPS II but may also be deficient in individuals with multiple sulfatase deficiency. Enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing variant in affected patients and subsequent carrier detection in female relatives (see MPS2Z / Hunter Syndrome, Full Gene Analysis, Varies). Currently, no clear genotype-phenotype correlations have been established.\(^{(1)}\)

**Useful For:** Diagnosis of mucopolysaccharidosis II (MPS II, Hunter syndrome) using dried blood spot specimens This test is not useful for determining carrier status for MPS II.

**Interpretation:** Results below 1.5 nmol/hour/mL in properly submitted specimens are consistent with iduronate-2-sulfatase deficiency (mucopolysaccharidosis II: MPS II, Hunter syndrome). If clinically indicated, consider further confirmation by molecular genetic analysis of the IDS gene. Note that this enzyme's activity can also be reduced in multiple sulfatase deficiency (MSD).\(^{(2)}\) If clinically indicated, consider biochemical genetic testing of other sulfatases or molecular genetic testing of the SUMF1 gene to exclude MSD. Normal results (> or =1.5 nmol/hour/mL) are not consistent with iduronate-2-sulfatase deficiency.

**Reference Values:**
> or =1.5 nmol/hour/mL

**Clinical References:**

**IFPCA**

**IF Additional (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**IFA26**

**IF Additional, Professional Only (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**IFTOA**

**IF Additional, Technical Only (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**IGAI**  
**70470**  
**IgA Immunostain, Technical Component Only**

**Clinical Information:** The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgA represents one of the immunoglobulin heavy chain types and is the major immunoglobulin class secreted at mucosal surfaces. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B-cell malignant lymphomas and multiple myeloma.

**Useful For:** Aiding in the classification of lymphomas and multiple myeloma

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**IGAS**  
**87938**  
**IgA Subclasses, Serum**

**Clinical Information:** IgA, the predominant immunoglobulin secreted at mucosal surfaces, consists of 2 subclasses, IgA1 and IgA2. IgA1 is the major (approximately 80%) subclass in serum. IgA2 is the major subclass in secretions such as milk. Although IgA deficiency is a common defect (1 in 700), it is...
usually asymptomatic. IgA deficiency with or without IgG subclass deficiency, however, can lead to recurrent pulmonary and gastrointestinal infections. Some infections (eg, recurrent sinopulmonary infections with Haemophilus influenzae) may be related to a deficiency of IgA2 in the presence of normal total IgA concentrations. Paradoxically, bacterial infections may also cause IgA deficiency. For example, IgA1 (but not IgA2) can be cleaved and inactivated by certain bacteria, thus depleting the majority of the IgA. In the presence of a concurrent IgA2 deficiency, infection by these organisms results in an apparent IgA deficiency. IgA deficiency is 1 cause of anaphylactic transfusion reactions. In these situations, IgA-deficient patients produce anti-IgA antibodies that react with IgA present in the transfusion product. While transfusion reactions typically occur in patients who have no detectable levels of IgA, they can occur in patients with measurable IgA. In these situations, the complete deficiency of 1 of the IgA subclasses may be the cause of the transfusion reactions.

**Useful For:** Investigation of immune deficiency due to IgA2 deficiency Evaluating patients with anaphylactic transfusion reactions

**Interpretation:** Low concentrations of IgA2 with normal IgA1 levels suggest an IgA2 deficiency. Elevated concentrations of IgA2 with normal or low amounts of IgA1 suggest a clonal plasma cell proliferative disorder secreting a monoclonal IgA2. Increased total IgA levels also may be seen in benign disorders (eg, infection, inflammation, allergy), hyper IgD syndrome with periodic fever and monoclonal gammopathies (eg, myeloma, monoclonal gammopathies of undetermined significance [MGUS]).

**Reference Values:**

**IgA**
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL

**IgA1**
- 0-<5 months: 10-34 mg/dL
- 5-<9 months: 14-41 mg/dL
- 9-<15 months: 20-50 mg/dL
- 15-<24 months: 24-58 mg/dL
- 2-<4 years: 16-162 mg/dL
- 4-<7 years: 17-187 mg/dL
- 7-<10 years: 21-221 mg/dL
- 10-<13 years: 27-250 mg/dL
- 13-<16 years: 36-275 mg/dL
- 16-<18 years: 44-289 mg/dL
- > or =18 years: 50-314 mg/dL

**IgA2**
- 0-<5 months: 0.4-5.5 mg/dL
- 5-<9 months: 1.5-6.2 mg/dL
- 9-<15 months: 2.8-7.0 mg/dL
- 15-<24 months: 3.9-7.7 mg/dL
- 2-<4 years: 1.3-31.1 mg/dL
- 4-<7 years: 1.1-39.1 mg/dL
- 7-<10 years: 1.4-48.0 mg/dL
- 10-<13 years: 2.6-53.4 mg/dL
- 13-<16 years: 4.7-55.1 mg/dL

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 1405

IGDI 70471

IgD Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgD represents one of the immunoglobulin heavy chain types. Immunoreactivity is a specific marker for B lymphocytes and plasma cells; it is expressed normally on mantle zone lymphocytes. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

Useful For: Aids in the classification of lymphomas and multiple myeloma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FIGEA 75618

IgE Receptor Antibody

Useful For: The test detects functional autoantibodies to the Fc-epsilon receptor (high affinity IgE receptor) or to IgE and is useful in the evaluation of chronic urticaria.

Interpretation: Chronic autoimmune urticaria (CIU) may be associated with autoantibodies to the high affinity IgE receptor (Fc-epsilon R1) or to IgE. In the presence of the autoantibodies, cross-linking of the Fc-epsilon-R1 receptor occurs, leading to basophil activation. The laboratory tests for the activation of donor basophils by CIU serum by analyzing the expression of the basophil specific ectoenzyme, CD203c. CD203c is upregulated on the surface of basophils following activation. A positive result is indicative of the presence of autoantibodies associated with CIU, but may also be due to other basophil-activating serum factors. Results must be correlated with clinical findings. The reference range was developed by the National Jewish Health Advanced Diagnostic Laboratories by analyzing 80 healthy control serum samples.

Reference Values: 0-12

**IgG Immunostain, Technical Component Only**

**Clinical Information:** The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgG represents one of the immunoglobulin heavy chain types. Immunoreactivity is a specific marker for B lymphocytes and plasma cells. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B-cell malignant lymphomas and multiple myeloma.

**Useful For:** Classification of lymphomas and multiple myeloma

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**IgG Subclasses, Serum**

**Clinical Information:** The most abundant immunoglobulin in human serum is immunoglobulin G (IgG) (approximately 80% of the total). IgG protein is comprised of molecules of 4 subclasses designated IgG1 through IgG4. Each subclass contains molecules with a structurally unique gamma heavy chain. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Molecules of different IgG subclasses have somewhat different biologic properties (eg, complement fixing ability and binding to phagocytic cells), which are determined by structural differences in gamma heavy chains. Clinical interest in IgG subclasses concerns potential immunodeficiencies (eg, subclass deficiencies) and IgG4-related diseases (eg, IgG4 elevations). This assay is best for deficiency testing, and the IgG4 assay (IGGS4 / Immunoglobulin Subclass IgG4, Serum) is best for IgG4-related disease testing. Diminished concentrations of IgG subclass proteins may occur in the context of hypogammaglobulinemia (eg, in common variable immunodeficiency where all immunoglobulin classes are generally affected) or deficiencies may be selective, usually involving IgG2. Deficiency of IgG1 usually occurs in patients with severe immunoglobulin deficiency involving other IgG subclasses. Deficiency of IgG2 is more heterogeneous and can occur as an isolated deficiency or in combination with deficiency of immunoglobulin A (IgA), or of IgA and other IgG subclasses. Most patients with IgG2 deficiency present with recurrent infections, usually sinusitis, otitis, or pulmonary infections. Children with deficiency of IgG2 often have deficient antibody responses to polysaccharide antigens including bacterial antigens associated with Haemophilus influenzae type B and Streptococcus pneumoniae. Isolated deficiencies of IgG3 or IgG4 occur rarely, and the clinical significance of these findings is not clear. IgG subclass 4-related disease is a recently recognized syndrome of unknown etiology most often occurring in middle-aged and older men. Several organ systems can be involved and encompasses many previous and newly described diseases such as type 1 autoimmune pancreatitis; Mikulicz disease and sclerosing sialadenitis; inflammatory orbital pseudotumor; chronic sclerosing aortitis; Riedel thyroiditis, a subset of Hashimoto thyroiditis; IgG4-related interstitial pneumonitis; and IgG4-related tubulointerstitial nephritis. Each of these entities is characterized by tumor-like swelling of the involved organs with infiltrative, predominately IgG4-positive, plasma cells with accompanying...
"storiform" fibrosis. In addition, elevated serum concentrations of IgG4 are found in 60% to 70% of patients diagnosed with IgG4-related disease. The diagnosis of IgG4-related disease requires a tissue biopsy of the affected organ demonstrating the aforementioned histological features. It is recommended that patients suspected of having an IgG4-related disease have their serum IgG4 level measured. Testing for IgG subclass levels may be indicated in patients with clinical evidence of a possible immunodeficiency with hypogammaglobulinemic patients or normal concentrations of total serum IgG.

**Useful For:** Second-order testing for evaluation of patients with clinical signs and symptoms of humoral immunodeficiency or combined immunodeficiency (cellular and humoral)

**Interpretation:** Diminished concentrations of all immunoglobulin G (IgG) subclasses are found in common variable immunodeficiency, combined immunodeficiency, ataxia telangiectasia, and other primary and acquired immunodeficiency diseases. A diminished concentration of IgG2 protein may be clinically significant in the context of recurrent sinopulmonary infection and may occur with or without concomitant immunoglobulin A deficiency. Elevated levels of IgG4 are consistent with, but not diagnostic of, IgG4-related disease. Slightly diminished concentrations of 1 or more IgG subclass proteins are not uncommon, and usually have little clinical significance. Conversely, some individuals with deficient specific antibody responses to polysaccharide antigens may have normal serum levels of IgG subclasses.

**Reference Values:**

**TOTAL IgG**
- 0-<5 months: 100-334 mg/dL
- 5-<9 months: 164-588 mg/dL
- 9-<15 months: 246-904 mg/dL
- 15-<24 months: 313-1,170 mg/dL
- 2-<4 years: 295-1,156 mg/dL
- 4-<7 years: 386-1,470 mg/dL
- 7-<10 years: 462-1,682 mg/dL
- 10-<13 years: 503-1,719 mg/dL
- 13-<16 years: 509-1,580 mg/dL
- 16-<18 years: 487-1,327 mg/dL
- > or =18 years: 767-1,590 mg/dL

**IgG1**
- 0-<5 months: 56-215 mg/dL
- 5-<9 months: 102-369 mg/dL
- 9-<15 months: 160-562 mg/dL
- 15-<24 months: 209-724 mg/dL
- 2-<4 years: 158-721 mg/dL
- 4-<7 years: 209-902 mg/dL
- 7-<10 years: 253-1,019 mg/dL
- 10-<13 years: 280-1,030 mg/dL
- 13-<16 years: 289-934 mg/dL
- 16-<18 years: 283-772 mg/dL
- > or =18 years: 341-894 mg/dL

**IgG2**
- 0-<5 months: < or =82 mg/dL
- 5-<9 months: < or =89 mg/dL
- 9-<15 months: 24-98 mg/dL
- 15-<24 months: 35-105 mg/dL
- 2-<4 years: 39-176 mg/dL
- 4-<7 years: 44-316 mg/dL
- 7-<10 years: 54-435 mg/dL
- 10-<13 years: 66-502 mg/dL
- 13-<16 years: 82-516 mg/dL
- 16-<18 years: 98-486 mg/dL
- > or =18 years: 171-632 mg/dL
**IgG3**

0-<5 months: 7.6-82.3 mg/dL  
5-<9 months: 11.9-74.0 mg/dL  
9-<15 months: 17.3-63.7 mg/dL  
15-<24 months: 21.9-55.0 mg/dL  
2-<4 years: 17.0-84.7 mg/dL  
4-<7 years: 10.8-94.9 mg/dL  
7-<10 years: 8.5-102.6 mg/dL  
10-<13 years: 11.5-105.3 mg/dL  
13-<16 years: 20.0-103.2 mg/dL  
16-<18 years: 31.3-97.6 mg/dL  
> or =18 years: 18.4-106.0 mg/dL

**IgG4**

0-<5 months: < or =19.8 mg/dL  
5-<9 months: < or =20.8 mg/dL  
9-<15 months: < or =22.0 mg/dL  
15-<24 months: < or =23.0 mg/dL  
2-<4 years: 0.4-49.1 mg/dL  
4-<7 years: 0.8-81.9 mg/dL  
7-<10 years: 1.0-108.7 mg/dL  
10-<13 years: 1.0-121.9 mg/dL  
13-<16 years: 0.7-121.7 mg/dL  
16-<18 years: 0.3-111.0 mg/dL  
> or =18 years: 2.4-121.0 mg/dL


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**IgG, Serum**

**Clinical Information:** Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) such as multiple sclerosis (MS), neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis may be due to local (intrathecal) synthesis of IgG. Elevations of CSF IgG or the CSF/serum IgG ratio may also occur as a result of permeability of the blood brain barrier, and hence, a correction using albumin measurements in CSF and serum is appropriate. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.

**Useful For:** Aiding in the diagnosis of multiple sclerosis and other CNS inflammatory conditions

**Interpretation:** Cerebrospinal fluid (CSF) IgG synthesis rate indicates the rate of increase in the daily CSF production of IgG in milligrams per day. A result greater than 12 mg/24h is elevated. A CSF index greater than 0.85 is elevated and indicative of increased synthesis of IgG.

**Reference Values:**

Only orderable as part of a profile. For more information see SFIG / Cerebrospinal Fluid (CSF) IgG Index Profile, Serum and Spinal Fluid.

0-4 months: 100-334 mg/dL  
5-8 months: 164-588 mg/dL
9-14 months: 246-904 mg/dL
15-23 months: 313-1,170 mg/dL
2-3 years: 295-1,156 mg/dL
4-6 years: 386-1,470 mg/dL
7-9 years: 462-1,682 mg/dL
10-12 years: 503-1,719 mg/dL
13-15 years: 509-1,580 mg/dL
16-17 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL


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**CASF 8271**

**IgG/Albumin Ratio, Spinal Fluid**

**Clinical Information:** Elevation of IgG levels in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) (multiple sclerosis: MS, neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to local CNS synthesis of IgG. The 2 most commonly used diagnostic laboratory tests for MS are CSF index and oligoclonal banding. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is therefore an indicator of the relative amount of CSF IgG compared to serum and any increase in the index is a reflection of IgG production in the central nervous system. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases.

**Useful For:** Assessment of cerebrospinal fluid (CSF) IgG/albumin ratio in the absence of a paired CSF and serum specimen

**Interpretation:** Cerebrospinal fluid IgG index is positive (elevated) in approximately 80% of patients with multiple sclerosis.

**Reference Values:**
- CSF IgG: 0.0-8.1 mg/dL
- CSF albumin: 0.0-27.0 mg/dL
- CSF IgG/albumin: 0.00-0.21


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**FG4FI 57851**

**IgG4 Food Panel I**

Current as of June 14, 2021 12:13 pm CDT   800-533-1710 or 507-266-5700 or mayocliniclabs.com
Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

FGFP2
57904

IgG4 Food Panel II

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

FG4FP
57591

IgG4 Food Panel VIII

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

IGG4I
70472

IgG4 Immunostain, Technical Component Only

Clinical Information: Immunoglobulin G4 is the least abundant of IgG subclasses, normally comprising 6% of total IgG. Elevated serum IgG4 levels may be associated with localized or systemic allergic and autoimmune manifestations, such as inflammatory pseudotumor in liver, breast, and lung, sclerosing pancreatitis, and pemphigus vulgaris. In these disease states, increased numbers of IgG4-positive plasma cells are present in the tissue.

Useful For: Identification of IgG4-positive plasma cells in the tissue of patients with systemic autoimmune or allergic manifestations

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

IGH Somatic Hypermutation Analysis, B-Cell Chronic Lymphocytic Leukemia (B-CLL), Varies

**Clinical Information:** During early B-cell development, IGH genes are assembled from multiple polymorphic gene segments that undergo rearrangements and selection, generating variable diversity joining (VDJ) combinations that are unique in both length and sequence for each B cell. In addition, new acquired (somatic) point variations are introduced into the variable (V) regions of mature B cells during the germinal center reaction in lymph nodes, and this process is called somatic hypermutation (SHM). Since chronic lymphocytic leukemia (CLL) originates from the malignant transformation of single lymphoid cells, each daughter cell shares 1 or (sometimes) more unique "clonal" antigen receptor gene rearrangements, which are cell and, therefore, tumor specific (ie, a tumor cell "fingerprint"). Clonal IGHV gene hypermutation status provides important prognostic information for patients with CLL and small lymphocytic lymphoma (SLL). The presence of IGH SHM is defined as greater than 2% difference from the germline VH gene sequence identity (mutated), whereas less than or equal to 2% difference is considered no SHM (unmutated). The status of SHM has clear influence on the median survival of CLL patients. Hypermutation of the IGH variable region is strongly predictive of a good prognosis, while lack of variants predicts a poorer prognosis.

**Useful For:** Providing prognostic information in patients with newly diagnosed B-cell chronic lymphocytic leukemia. This test is not intended for use in providing prognostic information for patients with other B-cell neoplasms or hematopoietic tumors.

**Interpretation:** The presence or absence of somatic hypermutation (SHM) in the immunoglobulin heavy chain gene (IGH) variable (V) region DNA will be reported. A variation frequency of greater than 2% will be reported as mutated. Both the percent mutation and the V region allele identified in the rearrangement will be included in the report. B-cell chronic lymphocytic leukemia (B-CLL) lacking SHM of the IGH V region (unmutated) is associated with a significantly worse prognosis than B-CLL containing SHM of the IGH V region (mutated).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**IGM Immunostain, Technical Component Only**

**Clinical Information:** The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgM represents one of the immunoglobulin heavy chain types. IgM positive-B lymphocytes are normally present in the follicular mantle zones and germinal centers. Immunoreactivity is a specific marker for B lymphocytes and plasma cells. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

**Useful For:** Classification of lymphomas and multiple myeloma

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate...
immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**IHPCA**

113298  **IHC Additional (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**IHA26**

113300  **IHC Additional, Professional Only (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**IHTOA**

113209  **IHC Additional, Tech Only (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**IHPCI**

113297  **IHC Initial (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**IHC26**

113299  **IHC Initial, Professional Only (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**IHTOI**

113208  **IHC Initial, Tech Only (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.
IHMPC 113301
IHC Multiplex (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHM26 113302
IHC Multiplex, Professional Only (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHMT0 113211
IHC Multiplex, Tech Only (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IMRGF 35276
Imatinib Mesylate Responsive Genes, FISH, Varies
Clinical Information: Myeloid neoplasms are primary disorders of the bone marrow cells. These malignancies encompass several entities with extremely varied clinical courses, including acute myeloid leukemias (AML), chronic myeloproliferative disorders (CMPD), and myelodysplastic syndromes. The underlying genetic mechanisms associated with these malignancies are varied and only a portion of the genetic abnormalities have targeted therapies clinically available. One group of genes, including ABL1 (Abelson murine leukemia viral oncogene homolog 1), ABL2 (Abelson murine leukemia viral oncogene homolog 2), PDGFRA (platelet-derived growth factor receptor, alpha), and PDGFRB (platelet-derived growth factor receptor, beta) can be inappropriately activated via various genetic mechanisms and result in overexpression of their tyrosine kinase activity. Tyrosine kinase activity plays an important role in cellular signaling, division, and differentiation; overexpression may cause some cancers. The myeloid malignancies associated with these aberrantly expressed genes include AML, chronic myelogenous leukemia (CML), hypereosinophilic syndrome/systemic mast cell disease (HES/SMCD), and atypical CMPD. These translocations can also be seen in lymphoid neoplasms, including acute lymphoblastic leukemia (ALL) and lymphomas, and they can also possess a varied genetic etiology. Several clinical studies have demonstrated that the malignancies displaying overexpression of these genes are responsive to imatinib mesylate, a drug that specifically targets these genes.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with acute leukemia or other myeloid malignancies Tracking known chromosome abnormalities and response to therapy in patients with myeloid malignancies

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Imipramine and Desipramine, Serum

Clinical Information: Imipramine and its metabolite desipramine are tricyclic antidepressants used to treat endogenous depression requiring 1 to 3 weeks of treatment before therapeutic effectiveness becomes apparent. Desipramine is used for treatment of endogenous depression when the patient needs a drug with significant stimulatory side effects. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Imipramine: The optimal dosage of imipramine yields trough (just before the next dose) blood levels of imipramine and desipramine combined from 175 to 300 ng/mL. If desipramine is given, no imipramine should be detected and the therapeutic concentration for desipramine alone is 100 to 300 ng/mL. Toxicity associated with imipramine is characterized by QRS widening leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations or at therapeutic concentrations in the early state of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 400 ng/mL. Desipramine: Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects, such as dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations in excess of 400 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 400 ng/mL.

Useful For: Monitoring imipramine and desipramine concentrations during therapy Evaluating potential imipramine and desipramine toxicity The test may also be useful to evaluate patient compliance

Interpretation: Most individuals display optimal response to imipramine when combined serum levels of imipramine and desipramine are between 175 and 300 ng/mL. Risk of toxicity is increased with levels above 400 ng/mL. Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Risk of toxicity is increased with desipramine levels above 400 ng/mL. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range, thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimen collected at trough (ie, immediately before the next dose).

Reference Values:
IMIPRAMINE AND DESIPRAMINE
Total therapeutic concentration: 175-300 ng/mL

DESIPRAMINE ONLY
Therapeutic concentration: 100-300 ng/mL
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


Immunofixation Heavy Chain Type Delta and Epsilon, Serum

Clinical Information: Monoclonal gammopathies indicate a clonal expansion of plasma cells or mature B lymphocytes and rarely may consist of IgD or IgE immunoglobulin heavy chains. The monoclonal gammopathies of such diseases include: multiple myeloma, primary systemic amyloidosis,
light-chain deposition disease, as well as the premalignant disorders of smoldering myeloma and monoclonal gammopathy of undetermined significance (MGUS). Monoclonal gammopathy patients may have a relatively small monoclonal protein abnormality or a large quantifiable peak (M-spike) on serum or urine protein electrophoresis. Abnormalities detected on serum protein electrophoresis (SPEP) should be immunotyped to confirm and characterize the monoclonal protein. Immunotyping of monoclonal proteins is usually done by immunofixation electrophoresis (IFE), which identifies the monoclonal immunoglobulin heavy-chain (gamma, alpha, mu, delta, or epsilon) and/or light-chain type (kappa or lambda). It is generally recommended that both SPEP and IFE be used as a screening panel. Because IFE is more sensitive than SPEP, IFE is not only recommended as part of the initial screening process but also for confirmation of complete response to therapy. Patients that have only lambda or kappa light chains on traditional IgG, IgA, IgM, kappa and lambda IFE should be tested using anti sera against IgD and IgE to accurately isotype the M-protein.

**Useful For:** Identification and isotyping of monoclonal immunoglobulin heavy (IgD and IgE) and light chains Documentation of complete response to therapy

**Interpretation:** Immunofixation impression comments are made based on visual interpretation of gels.

**Reference Values:**
Immunofixation Delta and Epsilon: No monoclonal IgD or IgE protein detected.
Immunofixation Delta and Epsilon, Flag: Negative

**Clinical References:**

**IMFXO 800316**

**Immunofixation Only, Serum**

**Clinical Information:** Monoclonal gammopathies indicate a clonal expansion of plasma cells or mature B lymphocytes. The monoclonal gammopathies include diseases such as multiple myeloma, Waldenstrom macroglobulinemia, lymphoproliferative disease, primary systemic amyloidosis, light-chain deposition disease, as well as the premalignant disorders of smoldering myeloma and monoclonal gammopathy of undetermined significance (MGUS). Monoclonal gammopathy patients may have a relatively small monoclonal protein abnormality or a large quantifiable peak (M-spike) on serum or urine protein electrophoresis. Abnormalities detected on serum protein electrophoresis (SPE) should have immunotyping performed to confirm and characterize the monoclonal protein. Immunotyping of monoclonal proteins is usually done by immunofixation electrophoresis (IFE) and identifies the monoclonal immunoglobulin heavy-chain (gamma, alpha, mu, delta, or epsilon) and/or light-chain type (kappa or lambda). It is generally recommended that both SPE and IFE be used as a screening panel. Because IFE is more sensitive than SPE, IFE is not only recommended as part of the initial screening process but also for confirmation of complete response to therapy. Because IFE is more sensitive than SPE, IFE is not only recommended as part of the initial screening process but also for confirmation of complete response to therapy.

**Useful For:** Identification of monoclonal immunoglobulin heavy and light chains Documentation of complete response to therapy

**Interpretation:** Immunofixation electrophoresis (IFE) is primarily performed to identify and characterize the presence of any monoclonal immunoglobulin heavy and/or light chains. Immunofixation impression comments are made based on visual interpretation of gels.

**Reference Values:**
Immunofixation: No monoclonal protein detected
Immunofixation Flag: Negative


Immunofixation with Free Light Chains, Quantitative, Urine

Interpretation: Results of urine free light chain testing can be used to monitor disease progression or response to therapy in patients for whom urine electrophoresis is unable to provide reliable Bence Jones Protein quantification. The results of urine kappa and lambda free light chain quantitative values may be misleading in specimens with high levels of urinary polyclonal free light chains, and absent Bence Jones protein by immunofixation; therefore correlation with urine immunofixation is required to identify inconsistent results. Total urinary protein is determined turbidimetrically by adding the albumin and kappa and/or lambda light chains. This value may not agree with the total protein as determined by chemical methods, which characteristically underestimates urinary light chains.

Reference Values:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein</td>
<td>Less than 150 mg/d</td>
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<tr>
<td>Free Urinary Kappa Light Chains</td>
<td>0.00-32.90 mg/L</td>
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<td>Free Urinary Kappa Excretion/Day</td>
<td>By report</td>
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<td>Free Urinary Lambda Light Chain</td>
<td>0.00-3.79 mg/L</td>
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<td>Free Urinary Lambda Excretion/Day</td>
<td>By report</td>
</tr>
<tr>
<td>IFE Interpretation</td>
<td>By report</td>
</tr>
</tbody>
</table>

Immunofixation, CSF

Reference Values:
Reference Range: No Monoclonal Proteins Detected

Immunofixation, Serum

Clinical Information: Immunotyping of monoclonal (M-) proteins identifies the monoclonal immunoglobulin heavy chain type (gamma, alpha, mu, delta or epsilon) and light chain type (kappa or lambda) in serum.

Useful For: Aids in diagnosis of monoclonal gammopathies when used in conjunction with urine monoclonal studies Identification and isotyping of monoclonal immunoglobulin heavy and light chains Documentation of complete response to therapy

Interpretation: If present, a characteristic monoclonal band (M-spike) is most often found in the gamma region on serum protein electrophoresis (PEL) and, occasionally, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein. Immunofixation electrophoresis (IFE) is primarily performed to
identify and characterize the presence of any monoclonal immunoglobulin heavy or light chains. Immunofixation impression comments are made based on visual interpretation of gels.

**Reference Values:**
Only orderable as part of a profile. For more information see MPSS / Monoclonal Protein Study, Serum.

- Immunofixation: No monoclonal protein detected
- Flag, Immunofixation: Negative

**Clinical References:**

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**Immunoglobulin A (IgA) Heavy and Light Chain (HLC) Pairs, Kappa and Lambda with Ratio**

**Clinical Information:** Elevated serum concentrations of monoclonal protein are indicative of an underlying abnormality, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and other lymphoproliferative disorders. International guidelines recommend serum protein electrophoresis (SPE) densitometry to be performed to quantify monoclonal proteins. However, monoclonal IgA proteins can often be obscured by other proteins in the Beta region of a SPE gel, making quantification inaccurate. Nephelometry can be used in these instances to measure total IgA, but this will include nontumor immunoglobulin, and measurement of either IgA Kappa or IgA Lambda may give a more accurate representation of tumor production. Furthermore, measurement of both IgA Kappa and IgA Lambda, calculation of the IgA Kappa:IgA Lambda ratio and comparison with values found in normal subjects can give a more sensitive indication of clonality. Use of the IgA Kappa:IgA Lambda ratio will also compensate for any changes in plasma volume.

**Useful For:** For the quantitative measurement of human IgA heavy chain and light chain intact immunoglobulin in serum. The result can be used when monitoring previously diagnosed IgA multiple myeloma patients and is used in conjunction with other clinical and laboratory findings. Heavy and light chain pair quantitation may be useful for:
1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin patterns on serum protein electrophoresis.
2. Quantitating monoclonal IgA proteins that are difficult to quantitate using serum protein electrophoresis alone.
3. Providing a more specific quantitation of the monoclonal protein than total IgA measurements alone.

**Interpretation:** An elevated IgA heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgA Kappa clone of plasma cells. A low IgA HLC pair ratio suggests a clonal proliferation of an IgA Lambda clone of plasma cells.

**Reference Values:**
- IgA Kappa (g/L): 0.48-2.82
- IgA Lambda (g/L): 0.36-1.98
- IgA Kappa:IgA Lambda ratio: 0.80-2.04

**Clinical References:**
**Immunoglobulin A (IgA), Serum**

**Clinical Information:** The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 15% is immunoglobulin A (IgA). Monoclonal gammapathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgA characterize multiple myeloma. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detection or monitoring of IgA monoclonal gammapathies and IgA-related immune deficiencies

**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin A may occur in monoclonal gammapathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammpathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

**Reference Values:**
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL

**Clinical References:**

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**Immunoglobulin D (IgD), Serum**

**Clinical Information:** Antibodies or immunoglobulins (Ig) are formed by plasma cells as a humoral immune response to antigens. The first antibodies formed after antigen stimulation are of the IgM class, followed later by IgG and also IgA antibodies. IgD normally occurs in serum in trace amounts. Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic diseases (chronic hepatitis, liver cirrhosis), acute and chronic infections, autoimmune diseases, as well as in the cord blood of neonates with intrauterine and perinatal infections. Increases in serum immunoglobulin concentration are seen in monoclonal gammapathies such as multiple myeloma, Waldenstrom macroglobulinemia, primary amyloidosis, and monoclonal gammpathy of undetermined significance. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies including advanced monoclonal gammpathies, lymphatic leukemia, and advanced malignant tumors. Changes in IgD concentration are used as a marker of changes in the size of the clone of monoclonal IgD plasma.
cells.

**Useful For:** Providing important information on the humoral immune status.

**Interpretation:** The physiologic significance of serum IgD concentration is unclear and in many normal persons serum IgD is undetectable. Increased concentrations may be due to polyclonal (reactive) or monoclonal plasma cell proliferative processes. A monoclonal IgD protein is present in 1% of patients with myeloma. Monoclonal IgD proteins are often in low concentrations and do not have a quantifiable M-peak on serum protein electrophoresis. However, the presence of an IgD monoclonal protein is almost always indicative of a malignant plasma cell disorder such as multiple myeloma or primary amyloidosis.

**Reference Values:**
< or =10 mg/dL

**Clinical References:**

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**Immunoglobulin E (IgE), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE that is present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE are generally thought of in the context of allergic disease. However, increases in the amount of circulating total serum IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease, except for allergic bronchopulmonary aspergillosis (ABPA). ABPA is a hypersensitivity reaction against the fungi Aspergillus that occurs most frequently in patients with asthma or cystic fibrosis. An elevation of total IgE is part of the diagnostic criteria for ABPA, although the specific diagnostic concentration is dependent on certain patient characteristics. For patients with an established diagnosis of allergic disease, measurement of total IgE is necessary for identification of candidates for omalizumab (anti-IgE) therapy and for determination of proper dosing. In addition to specific patient demographics and clinical presentations, candidates for omalizumab must have total IgE concentrations between 30 and 700 KU/L.

**Useful For:**
- Evaluation of patients with suspected diseases associated with elevations in total immunoglobulin E (IgE), including allergic disease, primary immunodeficiencies, infections, malignancies, or other inflammatory diseases
- Diagnostic evaluation of patients with suspected allergic bronchopulmonary aspergillosis
- Identification of candidates for omalizumab (anti-IgE) therapy

**Interpretation:** Elevated concentrations of total immunoglobulin E (IgE) may be found in a variety of clinical diseases including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Elevated total IgE concentrations may be consistent with a diagnosis of allergic bronchopulmonary aspergillosis, provided other laboratory and clinical criteria are fulfilled. Total IgE concentrations between 30 to 700 KU/L may identify candidates for omalizumab therapy and may
help to determine proper therapeutic dosing.

**Reference Values:**

Results reported in kU/L

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<tbody>
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<td>4-6 years</td>
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<td>7 and 8 years</td>
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</tbody>
</table>


**Immunoglobulin Free Light Chains, Serum**

**Clinical Information:** The monoclonal gammopathies are characterized by a clonal expansion of plasma cells that secrete a monoclonal immunoglobulin. The monoclonal immunoglobulin secreted by these cells serves as a marker of the clonal proliferation and the quantitation of monoclonal protein can be used to monitor the disease course. The monoclonal gammopathies include multiple myeloma (MM), light chain multiple myeloma (LCMM), Waldenstrom macroglobulinemia (WM), nonsecretory multiple myeloma (NSMM), smoldering multiple myeloma (SMM), monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis (AL), and light chain deposition disease (LCDD). Monoclonal proteins are typically detected by serum protein electrophoresis and immunofixation (IF). However, the monoclonal light chain diseases (LCMM, AL, LCDD) and NSMM often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by protein electrophoresis. A sensitive nephelometric assay specific for kappa free light chain (FLC) and lambda FLC that doesn't recognize light chains bound to immunoglobulin heavy chains has recently been described. This automated, nephelometric assay is reported to be more sensitive than IF for detection of monoclonal FLC. In some patients with NSMM, AL, or LCDD, the FLC assay provides a positive identification of a monoclonal serum light chain when the serum IF is negative. In addition, the quantitation of FLC has been correlated with disease activity in patients with NSMM and AL. The following algorithms are available in Special Instructions: -Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Monitoring serum from patients with monoclonal light chain diseases without a M-spike on protein electrophoresis

**Interpretation:** The specificity of this assay for detection of monoclonal light chains relies on the
ratio of free kappa and lambda (K/L) light chains. Once an abnormal free light chain (FLC) K/L ratio has been demonstrated and a diagnosis has been made, the quantitation of the monoclonal light chain is useful for monitoring disease activity. Changes in FLC quantitation reflect changes in the size of the monoclonal plasma cell population. Our experience to date is limited, but changes of more than 25% or trending of multiple specimens are needed to conclude biological significance.

**Reference Values:**

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA FLC RATIO
0.26-1.65

**Clinical References:**

**Immunoglobulin Free Light Chains, Serum**

**Clinical Information:** The monoclonal gammopathies are characterized by a clonal expansion of plasma cells that secrete a monoclonal immunoglobulin. The monoclonal immunoglobulin secreted by these cells serves as a marker of the clonal proliferation, and the quantitation of monoclonal protein can be used to monitor the disease course. The monoclonal gammopathies include multiple myeloma (MM), light chain multiple myeloma (LCMM), Waldenstrom macroglobulinemia (WM), nonsecretory multiple myeloma (NSMM), smoldering multiple myeloma (SMM), monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis (AL), and light chain deposition disease (LCDD). The monoclonal light chain diseases (LCMM, AL, LCDD and NSMM) often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by serum protein electrophoresis. An elevated ratio of kappa to lambda free light chains (FLC K/L) indicates a monoclonal kappa FLC, and an abnormally low FLC K/L indicates a monoclonal lambda FLC. The kappa and lambda FLC may both be elevated in the sera of patients with polyclonal hypergammaglobulinemia, but the FLC K/L is normal. If a patient has an abnormal serum FLC K/L ratio but has no serum monoclonal protein detected by immunofixation, a urine monoclonal protein study (eg, immunofixation) should be performed and the serum immunofixation should be repeated. The FLC K/L ratio may be useful as a diagnostic test in patients in whom immunofixation for serum monoclonal light chains is negative and in whom there is a suspicion of primary systemic amyloidosis, light chain deposition disease, or non-secretory myeloma. The quantitation of kappa or lambda immunoglobulin free light chains may be used to monitor disease activity in patients with monoclonal light chain diseases without a serum M-spike.Â The following algorithms are available in Special Instructions: -Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Monitoring serum from patients with monoclonal light chain diseases without a M-spike on protein electrophoresis May be useful as a diagnostic test in patients in whom there is a suspicion of primary systemic amyloidosis, light chain deposition disease, or non-secretory myeloma

**Interpretation:** The specificity of this assay for detection of monoclonal light chains relies on the ratio of free kappa and lambda (K/L) light chains. Once an abnormal free light chain (FLC) K/L ratio has been demonstrated and a diagnosis has been made, the quantitation of the monoclonal light chain is useful for
monitoring disease activity. Changes in FLC quantitation reflect changes in the size of the monoclonal plasma cell population. Our experience to date is limited, but changes of more than 25% or trending of multiple specimens are needed to conclude biological significance.

**Reference Values:**

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>KAPPA-FREE LIGHT CHAIN</td>
<td>0.33-1.94 mg/dL</td>
</tr>
<tr>
<td>LAMBDA-FREE LIGHT CHAIN</td>
<td>0.57-2.63 mg/dL</td>
</tr>
<tr>
<td>KAPPA/LAMBDA FLC RATIO</td>
<td>0.26-1.65</td>
</tr>
</tbody>
</table>

**Clinical References:**


**FHLCG 75551 Immunoglobulin G (IgG) Heavy and Light Chain (HLC) Pairs, Kappa and Lambda with Ratio**

**Clinical Information:** Elevated serum concentrations of monoclonal protein are indicative of an underlying abnormality, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and other lymphoproliferative disorders. International guidelines recommend serum protein electrophoresis or nephelometric immunoglobulin quantification as tools to monitor patients’ disease (alongside other tests including flow cytometry and serum free light chain analysis). Total IgG nephelometric assays will include nontumor immunoglobulin, and measurement of either IgG Kappa or IgG Lambda may give a more accurate representation of tumor production. Furthermore, measurement of both IgG Kappa and IgG Lambda, calculation of the IgG Kappa:IgG Lambda ratio, and comparison with values found in normal subjects can give a more sensitive indication of clonality. Additionally, changes in the IgG Kappa:IgG Lambda ratio and its normalization when compared to a normal ratio range should assist in monitoring patients’ disease. Use of the IgG Kappa:IgG Lambda ratio will also compensate for any changes in plasma volume and correct for half life variations due to receptor saturation.

**Useful For:** Heavy and light chain pair quantitation may be useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin patterns on serum electrophoresis. 2. Quantitating monoclonal IgG proteins that are difficult to quantitate using serum protein electrophoresis alone. 3. Providing a more specific quantitation of the monoclonal protein than total IgG measurements alone.

**Interpretation:** An elevated IgG heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgG Kappa clone of plasma cells. A low IgG HLC pair ratio suggests a clonal proliferation of an IgG Lambda clone of plasma cells.

**Reference Values:**

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG Kappa (g/L)</td>
<td>4.03 - 9.78</td>
</tr>
<tr>
<td>IgG Lambda (g/L)</td>
<td>1.97 - 5.71</td>
</tr>
<tr>
<td>IgG Kappa:IgG Lambda ratio</td>
<td>0.98 - 2.75</td>
</tr>
</tbody>
</table>

Immunoglobulin G (IgG) Subtypes Immunofluorescence, Tissue

Clinical Information: IgG subtypes are helpful in confirming some disease processes affecting the kidney.

Useful For: Determining the subclass of IgG antibody found in renal immunofluorescent panel and determining if the deposits are monoclonal or monotypic

Interpretation: Staining intensity is graded as negative (0), weak (trace, 1+), moderate (2+) and strong (3+) and will be reported as such when not accompanied by a pathology consultation request.


Immunoglobulin G (IgG), Serum

Clinical Information: The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is immunoglobulin G (IgG). Elevations of IgG may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgG characterize multiple myeloma. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detecting or monitoring of IgG monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin G may occur in monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:
- 0-<5 months: 100-334 mg/dL
- 5-<9 months: 164-588 mg/dL
- 9-<15 months: 246-904 mg/dL
- 15-<24 months: 313-1,170 mg/dL
- 2-<4 years: 295-1,156 mg/dL
- 4-<7 years: 386-1,470 mg/dL
- 7-<10 years: 462-1,682 mg/dL
- 10-<13 years: 503-1,719 mg/dL
- 13-<16 years: 509-1,580 mg/dL
- 16-<18 years: 487-1,327 mg/dL
- > or =18 years: 767-1,590 mg/dL

Immunoglobulin Gene Rearrangement, Blood

Clinical Information: The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the unrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B-cell or plasma cell population is polyclonal or monoclonal using peripheral blood specimens Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to one from a previous neoplastic specimen

Interpretation: An interpretive report will be provided. The interpretation of the presence or absence of a predominant Ig gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

Reference Values: An interpretive report will be provided.


Immunoglobulin Gene Rearrangement, PCR, Bone Marrow

Clinical Information: The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell or plasma cell has a unique rearrangement profile. Other cell types usually retain the unrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain identical Ig gene rearrangement profiles. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the
predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

**Useful For:** Determining whether a B-cell or plasma cell population is polyclonal or monoclonal in bone marrow specimens. Identifying neoplastic cells as having B-cell or plasma cell differentiation. Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to a previous neoplastic specimen.

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal B-cell population. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Immunoglobulin Kappa Free Light Chain, Spinal Fluid**

**Clinical Information:** Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). The clinical diagnosis of MS is centered on each individual patient, while applying diagnostic guidelines. Immunoglobulin free light chain (FLC) presence in cerebrospinal fluid (CSF) is an alternative for diagnosis of MS using nephelometry. Light chains are produced in excess during antibody formation and secreted from the plasma cells or plasma blasts. Quantitative FLC assays use antisera directed against epitopes that are exposed only when the light chains are free (unbound to heavy chain) in solution. FLC immunoassays can be used to specifically quantitate FLC even in the presence of large concentrations of polyclonal immunoglobulins. Routine use of isoelectric focusing electrophoresis coupled with IgG-specific immunoblotting (IgG-IEF) identifies immunoglobulins specific to the CNS. This method is part of the diagnostic criteria used in cases of MS, ie, oligoclonal banding (OLIG). However, OLIG / Oligoclonal Banding, Serum and Spinal Fluid is a labor-intensive technique that includes subjective interpretation of IgG bands from paired CSF and serum. This test, when considered positive at a concentration greater than or equal to 0.1000 mg/dL, as a medical decision point, has a sensitivity of 70% with a specificity of 87%, which is comparable in terms of sensitivity and specificity to oligoclonal banding. The differences between this FLC test and the OLIG analysis are not statistically significant. The MSP3 panel combines the ease of use and interpretation of the quantitative measurement of kappa free light chains in CSF and allies it to the traditional interpretation of oligoclonal bands for optimized efficiency in laboratory testing for demyelinating diseases and improved test utilization.

**Useful For:** Diagnosis of multiple sclerosis and other demyelinating conditions

**Interpretation:** When result is greater than or equal to 0.1000 mg/dL, the kappa free light chain concentration measured in cerebrospinal fluid (CSF) is at or greater than the threshold associated with demyelinating disease. This is a positive result. These findings, however, are not specific for multiple sclerosis (MS) because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). Clinical correlation is recommended. Automatic reflexing to oligoclonal bands will occur. When result is less than 0.0600 mg/dL, the kappa free light chain concentration measured in CSF is lower than the threshold associated with demyelinating disease. This is a negative result. Testing for oligoclonal banding is not performed. Clinical correlation is recommended. When result is from 0.0600 to 0.0999 mg/dL, the kappa free light chain concentration measured in CSF is slightly elevated but not above the medical decision point of 0.1000 mg/dL associated with demyelinating disease. This is a borderline result. Reflexing to oligoclonal bands will be automatically performed and clinical correlation is recommended.

**Reference Values:**
Only orderable as part of a profile. For more information see MSP3 / Multiple Sclerosis (MS) Profile, Serum and Spinal Fluid.

Medical decision point: 0.1000 mg/dL

**Clinical References:**

Immunoglobulin Kappa Free Light Chain, Spinal Fluid

Clinical Information: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). The clinical diagnosis of MS is centered on each individual patient, while applying diagnostic guidelines. Immunoglobulin free light chain (FLC) presence in cerebrospinal fluid (CSF) is an alternative for diagnosis of MS using nephelometry. Light chains are produced in excess during antibody formation and secreted from the plasma-cells or plasma-blasts. Quantitative FLC assays use antisera directed against epitopes that are exposed only when the light chains are free (unbound to heavy chain) in solution. FLC immunoassays can be used to specifically quantitate FLC even in the presence of large concentrations of polyclonal immunoglobulins. Routine use of isoelectric focusing electrophoresis coupled with IgG-specific immunoblotting (IgG-IEF) identifies immunoglobulins specific to the CNS. This method is part of the diagnostic criteria used in cases of MS, ie, oligoclonal banding (OLIG / Oligoclonal Banding, Serum and Spinal Fluid). However, oligoclonal banding is a labor-intensive technique that includes subjective interpretation of IgG bands from paired CSF and serum. This test, when considered positive at a concentration greater than or equal to 0.1000 mg/dL as a medical decision point, has a sensitivity of 70.4% with a specificity of 86.8%. The differences between this test and the oligoclonal banding analysis are not statistically significant (p=0.20) and the 2 tests show comparable performance. However, this test does not require a paired serum specimen, offers a shorter turnaround-time for results, and an objective quantitative result. This testing is most useful in patients presenting with a clinically isolated syndrome, which is a clinical episode where patient reports symptoms (headaches, optic neuritis, fatigue and many others, depending on the disease location) characteristic of inflammation and demyelination of the central nervous system, and need to be checked by a neurologist. This is when the likelihood of a diagnosis of multiple sclerosis is greater or most likely but not yet known or confirmed. CSF laboratory testing is also strongly recommended in cases where the imaging findings are atypical, and in populations in which multiple sclerosis is less common (eg, children, older individuals, or non-white populations).

Useful For: Diagnosis of multiple sclerosis and other demyelinating conditions Evaluation of patients presenting with a clinically isolated syndrome, which is a clinical episode where patient reports symptoms (headaches, optic neuritis, fatigue and many others, depending on the disease location) characteristic of inflammation and demyelination of the central nervous system A testing recommendation in cases where the imaging findings are atypical, and in populations in which multiple sclerosis is less common (eg, children, older individuals, or non-white populations) The test is not useful when a clear diagnosis is already known because a positive result does not correlate with severity of the disease or disease outcomes.

Interpretation: When result is less than 0.1000 mg/dL, the kappa free light chain concentration measured in CSF is lower than the threshold associated with demyelinating disease. This is a negative result. Clinical correlation recommended. When result is greater than or equal to 0.1000 mg/dL, the kappa free light chain concentration measured in CSF is at or greater than the threshold associated with demyelinating disease. This is a positive result. These findings, however, are not specific for multiple sclerosis (MS) because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). Clinical correlation recommended.
**Reference Values:**
Medical Decision Point: 0.1000 mg/dL


### Immunoglobulin M (IgM) Heavy and Light Chain (HLC) Pairs, Kappa and Lambda with Ratio

**Clinical Information:** Elevated serum concentrations of monoclonal protein are indicative of an underlying abnormality, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, Waldenström's macroglobulinemia and other lymphoproliferative disorders. Serum protein electrophoresis (SPE) densitometry is recommended to quantify monoclonal proteins. Nephelometry can also be used in these instances to measure total IgM, but this will include nontumor immunoglobulin, and measurement of either IgM Kappa or IgM Lambda may provide additional information regarding tumor production.

**Useful For:** Heavy and light chain pair quantitation may be useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin patterns on serum electrophoresis. 2. Quantitating monoclonal IgM proteins that are difficult to quantitate using serum protein electrophoresis alone. 3. Providing a more specific quantitation of the monoclonal protein than total IgM measurements alone.

**Interpretation:** An elevated IgM heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgM kappa clone of plasma cells. A low IgM HLC pair ratio suggests a clonal proliferation of an IgM lambda clone of plasma cells.

**Reference Values:**
IgM Kappa (g/L): 0.29-1.82
IgM Lambda (g/L): 0.17-0.94
IgM Kappa:IgM Lambda ratio: 0.96-2.30

**Immunoglobulin M (IgM), Serum**

**Clinical Information:** The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 5% is immunoglobulin M (IgM). Elevations of IgM may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgM occur in macroglobulinemia. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detecting or monitoring of IgM monoclonal gammopathies and IgM-related immune deficiencies

**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin M may occur in monoclonal gammopathies such as macroglobulinemia, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

**Reference Values:**

- 0-<5 months: 26-122 mg/dL
- 5-<9 months: 32-132 mg/dL
- 9-<15 months: 40-143 mg/dL
- 15-<24 months: 46-152 mg/dL
- 2-<4 years: 37-184 mg/dL
- 4-<7 years: 37-224 mg/dL
- 7-<10 years: 38-251 mg/dL
- 10-<13 years: 41-255 mg/dL
- 13-<16 years: 45-244 mg/dL
- 16-<18 years: 49-201 mg/dL
- > or =18 years: 37-286 mg/dL

**Clinical References:**


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**Immunoglobulin Subclass IgG4, Serum**

**Clinical Information:** The most abundant immunoglobulin (Ig) isotype in human serum is immunoglobulin G (IgG). IgG immunoglobulins are comprised of 4 subclasses designated IgG1 through IgG4. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Each IgG subclass contains structurally unique portions of the constant region of the gamma heavy chain. IgG subclass 4-related disease is a recently recognized syndrome of unknown etiology most often occurring in middle-aged and older men. Several organ systems can be involved and encompasses many previous and newly described diseases such as type I autoimmune pancreatitis; Mikulicz disease and sclerosing sialadenitis; inflammatory orbital pseudotumor; chronic sclerosing aortitis; Riedel thyroiditis, a subset of Hashimoto thyroiditis; IgG4-related interstitial pneumonitis; and IgG4-related tubulointerstitial nephritis.
Each of these entities is characterized by tumor-like swelling of the involved organs with infiltrative, predominately IgG4-positive, plasma cells with accompanying "storiform" fibrosis. In addition, elevated serum concentrations of IgG4 are found in 60% to 70% of patients diagnosed with IgG4-related disease. The diagnosis of IgG4-related disease requires a tissue biopsy of the affected organ demonstrating the aforementioned histological features. It is recommended that patients suspected of having an IgG4-related disease have their serum IgG4 level measured.

**Useful For:** Supporting the diagnosis of IgG4-related disease

**Interpretation:** Elevated levels of IgG4 are consistent with, but not diagnostic of, IgG4-related disease.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range (mg/dL)</th>
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<td>0-&lt;5 months</td>
<td>&lt; or =19.8</td>
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<td>5-&lt;9 months</td>
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<td>4-&lt;7 years</td>
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<tr>
<td>7-&lt;10 years</td>
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<td>10-&lt;13 years</td>
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</tr>
<tr>
<td>13-&lt;16 years</td>
<td>0.7-121.7</td>
</tr>
<tr>
<td>16-&lt;18 years</td>
<td>0.3-111.0</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>2.4-121.0</td>
</tr>
</tbody>
</table>

**Clinical References:**


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**Immunoglobulin Total Light Chains, Urine**

**Clinical Information:** Immunoglobulin light chains are usually cleared from blood through the renal glomeruli and reabsorbed in the proximal tubules so that urine light-chain concentrations are very low or undetectable. The production of large amounts of monoclonal light chains, however, can overwhelm this reabsorption mechanism. The detection of monoclonal light chains in the urine (Bence Jones proteinuria) has been used as a diagnostic marker for multiple myeloma since the report by Dr. H. Bence Jones in 1847. Current laboratory procedures employ protein electrophoresis and immunofixation for the identification and characterization of urine monoclonal light chains, and the monoclonal light chains may be present in large enough amounts to also be quantitated as an M-spike on protein electrophoresis. The electrophoretic M-spike is the recommended method of monitoring monoclonal gammopathies such as multiple myeloma. Monitoring the urine M-spike is especially useful in patients with light-chain multiple myeloma in whom the serum M-spike is very small or absent, but the urine M-spike is large. Just as quantitative serum immunoglobulins by immunonephelometry are a complement to M-spike quantitation by serum electrophoresis, this quantitative urine light-chain assay may be used to complement urine M-spike quantitation by electrophoresis.

**Useful For:** Monitoring patients whose urine demonstrates large M-spikes Confirming the quantitation of specimens that show M-spikes by electrophoresis Detecting urine monoclonal proteins and identification of specimens that need urine protein electrophoresis

**Interpretation:** A kappa/lambda (K/L) ratio greater than 6.2 suggests the presence of monoclonal kappa light chains. A K/L ratio less than 0.7 suggests the presence of monoclonal lambda light chains. In 24-hour specimens, a greater than 90% increase in concentration suggests progression or relapse; a greater than 90% decrease suggests treatment response. Increased kappa and/or lambda light chains may be seen in benign (polyclonal) and neoplastic (monoclonal) disorders.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current as of June 14, 2021 12:13 pm CDT</td>
<td>800-533-1710 or 507-266-5700 or mayocliniclabs.com</td>
</tr>
</tbody>
</table>
KAPPA TOTAL LIGHT CHAIN
<0.9 mg/dL

LAMBDA TOTAL LIGHT CHAIN
<0.7 mg/dL

KAPPA/LAMBDA RATIO
0.7-6.2


Immunoglobulins (IgG, IgA, and IgM), Serum

Clinical Information: The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is immunoglobulin G (IgG), 15% is immunoglobulin A (IgA), 5% is immunoglobulin M (IgM), 0.2% is immunoglobulin D (IgD), and a trace is immunoglobulin E (IgE). Elevations of IgG, IgA, and IgM may be due to polyclonal immunoglobulin production. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgG, IgA, IgD, and IgE characterize multiple myeloma. Monoclonal elevations of IgM occur in macroglobulinemia. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detecting or monitoring of monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevations of immunoglobulin G (IgG), immunoglobulin A (IgA), or immunoglobulin M (IgM) may occur in monoclonal gammopathies such as multiple myeloma (IgG, IgA), macroglobulinemia (IgM), primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:

IgG
0-5 months: 100-334 mg/dL
5-9 months: 164-588 mg/dL
9-15 months: 246-904 mg/dL
15-24 months: 313-1,170 mg/dL
2-4 years: 295-1,156 mg/dL
4-7 years: 386-1,470 mg/dL
7-10 years: 462-1,682 mg/dL
10-13 years: 503-1,719 mg/dL
13-16 years: 509-1,580 mg/dL
16-18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

IgA
0-5 months: 7-37 mg/dL
5-9 months: 16-50 mg/dL
9-15 months: 27-66 mg/dL
15-24 months: 36-79 mg/dL
2-4 years: 27-246 mg/dL
4-7 years: 29-256 mg/dL
Immunoglobulins, CSF Quantitative

Reference Values:
- Immunoglobulin M CSF (0.0 - 0.7) mg/dL
- Immunoglobulin G CSF (0.0 - 6.0) mg/dL
- Immunoglobulin A CSF (0.0 - 0.7) mg/dL

Infectious Mononucleosis, Rapid Test, Serum

Clinical Information: Infectious mononucleosis (IM) is a viral illness that involves reticuloendothelial tissue and is generally limited to children and young adults. IM is most commonly caused by Epstein-Barr virus (EBV). The disease is characterized by fever, sore throat, lymphadenopathy, headache, and fatigue and, on a symptomatic basis, may be confused with other diseases. Detectable levels of unique heterophile antibodies are produced in patients with IM.

Useful For: Rapid confirmation of a diagnosis of infectious mononucleosis

Interpretation: Detectable levels of the infectious mononucleosis (IM) heterophile antibody can usually be expected to occur between the sixth and tenth day following the onset of symptoms. The level usually increases through the second or third week of illness and, thereafter, can be expected to persist, gradually declining over a 12-month period.

Reference Values:
- Negative
  - Reference values apply to all ages.
Inflammatory Bowel Disease Primary Immunodeficiency (PID) Panel, Varies

Clinical Information: Inflammatory bowel disease (IBD) is a term used to encompass disorders involving chronic intestinal inflammation. These conditions are typically classified as either Crohn's disease or ulcerative colitis based on clinical features, colonoscopy findings, histologic changes, and the anatomical distribution of disease; however, in some cases, overlapping features are noted. Over the past few decades, the incidence of inflammatory bowel disease has been rapidly increasing in both children and adults. Common symptoms include: diarrhea, abdominal pain, fatigue, and unintentional weight loss. The majority of IBD is thought to be either polygenic or multifactorial. In these susceptible individuals, an environmental component appears to trigger disease manifestation. However, in rare cases, IBD or IBD-like intestinal inflammation can be attributed to disease-causing variants in a single gene (monogenic inheritance) which results in a highly penetrant condition. Monogenic IBD typically presents at a very young age (often <6 years of age at onset of symptoms) compared to polygenic IBD (peak at 20-40 years of age), although the incidence of polygenic IBD in young patients is increasing and conversely some patients with milder forms of monogenic IBD may not present until later. Individuals with polygenic or monogenic IBD may also have other family members affected with IBD (a positive family history). In many cases, patients with a monogenic form of IBD may not respond well to conventional treatment modalities and may have a related primary immunodeficiency. Identification of the genetic cause of disease in these individuals is important as it may change the treatment plan for these individuals. Depending on the genetic cause, targeted therapies or allogeneic hematopoietic stem cell transplantation may be beneficial. Therefore, identification of these conditions is important as it can guide treatment, including medical therapy, surgery, or stem cell transplant, and may reduce the high morbidity and mortality associated with these conditions.

Useful For: Genetic testing for patients with very early onset inflammatory bowel disease (IBD), early onset IBD, or IBD refractory to treatment. Identifying variants in genes known to be associated with monogenic IBD or IBD-like conditions. Identification may allow for development of a specific treatment and surveillance plan for these patients based on the molecular alteration identified, and predictive testing of at-risk family members. Diagnosis of monogenic IBD or IBD-like conditions among patients with early onset or very-early onset IBD, or who are refractory to conventional therapy. Ascertainment of carrier status of family members of individuals diagnosed with early onset IBD for genetic counseling purposes. If a family member has already tested positive for a variant in a gene on this panel, order known variant analysis (KVAR). See Ordering Guidance section (Specimen tab) for more details. This test is not useful for establishing a diagnosis of typical polygenic IBD or for differentiating between Crohn’s disease and ulcerative colitis.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

Inflammatory Myofibroblastic Tumors (IMT), 2p23 (ALK) Rearrangement, FISH, Tissue

Clinical Information: Inflammatory myofibroblastic tumor (IMT) is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils which occur primarily in the soft tissue and viscera of children and young adults. They may arise in any anatomical site including lung, soft tissue, retroperitoneum, and bladder. The genetic mechanisms underlying IMT pathogenesis are only partially known, but cytogenetic analyses have disclosed chromosomal rearrangements involving the ALK gene at 2p23. Studies support that identification of ALK gene rearrangement is useful to differentiate IMTs from other spindle cell neoplasms of soft tissue and viscera.

Useful For: Supporting the diagnosis of inflammatory myofibroblastic tumor when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result is consistent with a subset of inflammatory myofibroblastic tumor (IMT). A negative result suggests that an ALK gene rearrangement is not present but does not exclude the diagnosis of IMT.

Reference Values:
An interpretive report will be provided.


Infliximab Quantitation with Reflex to Antibodies to Infliximab, Serum

Clinical Information: Infliximab (Remicade, Renflexis, Inflectra) is a chimeric immunoglobulin (IgG1 kappa) targeting tumor necrosis factor-alpha (TNF-a), and it is currently FDA-approved for the treatment of multiple inflammatory conditions. Infliximab binds to soluble TNF-a and transmembrane homotrimers, which are found on the surface of macrophages and T-cells, with similar affinity. Infliximab has the ability to mediate complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity, which leads to the lysis of target cells. Infliximab pharmacokinetic properties may vary with disease and clearance is affected by concomitant use of immunosuppressants, high concentrations of TNF-a and C-reactive proteins, low albumin concentrations, high body mass index, and presence of antibodies to infliximab (ATI), also known as human antichimeric antibodies (HACA). Males seem to clear infliximab faster than females. Several studies have demonstrated that infliximab quantitation in the setting of loss of response to therapy can aid in patient management, as trough concentrations defined as therapeutic have been associated with superior clinical response and
Evaluation of infliximab concentrations may be of value for all inflammatory diseases for which it is prescribed. Primary indications for testing of infliximab include loss of response, partial response on initiation of therapy, autoimmune or hypersensitivity reactions, primary nonresponse, reintroduction after drug holiday, endoscopic/computed tomography enterography recurrence (in inflammatory bowel disease), and acute infusion reactions. Measurement of infliximab concentrations is indicated at trough, immediately prior to the next scheduled infusion. Low trough concentrations may be correlated with loss of response to infliximab. Assessment of antibodies to infliximab is suggested when infliximab quantitation at trough is 5.0 mcg/mL or less. Infliximab concentrations tend to stabilize after 14 weeks (approximately 100 days). Quantitation of peak infliximab concentrations is strongly discouraged. The ATI assay has been verified to analyze infliximab and infliximab-dyyb (Inflectra, Pfizer Inc) with no analytical differences between the 2 drugs quantitation. Inflectra has the same primary amino acid sequence as Remicade and Renflexis. Therefore, "infliximab" will be used to refer to both the reference product and the biosimilar product interchangeably. A biosimilar product is a biological product that is approved based on showing that it is highly similar to an FDA-approved biological product, known as the reference product. No clinically meaningful differences in terms of safety and effectiveness from the reference product are present. Only minor differences in clinically inactive components are allowable in biosimilar products. In contrast to generic medications, a prescription of biosimilars needs to come from the ordering physician and not the dispensing pharmacy (pharmacies cannot substitute a biosimilar for another medication; a separate prescription is required).

**Useful For:** Trough level quantitation for evaluation of patients with loss of response to infliximab and infliximab-dyyb

**Interpretation:** Low trough concentrations may be correlated with loss of response to infliximab. For infliximab trough concentrations 5.0 mcg/mL or less, testing for antibodies to infliximab (ATI) is suggested. For infliximab trough concentrations above 5.0 mcg/mL, the presence of ATI is unlikely; patients experiencing loss of response to infliximab may benefit from an increased dose or a shorter infusion interval. Results above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough.

**Reference Values:**

**INFLIXIMAB QUANTITATION:**
Limit of quantitation is 1.0 mcg/mL. Therapeutic ranges are disease specific.

Pediatric reference ranges are not established.

**INFLIXIMAB ANTIBODIES**
Absence of antibodies to infliximab (ATI) is defined as <50 U/mL.
Presence of ATI is reported as positive when concentrations are > or =50 U/mL.

**Influenza A and B, PCR, Varies**

**Clinical Information:** Influenza, or the flu, is a contagious viral infection of the respiratory tract. Transmission of influenza is primarily airborne (ie, coughing or sneezing), and the peak of transmission usually occurs in the winter months. Symptoms commonly include fever, chills, headache, muscle aches, malaise, cough, and sinus congestion. Gastrointestinal symptoms (ie, nausea, vomiting, or diarrhea) may also occur, primarily in children but are less common in adults. Symptoms generally appear within 2 days of exposure to a person who's been infected. Pneumonia may develop as a complication of influenza, causing increased morbidity and mortality in pediatric, elderly, and immunocompromised populations. Influenza viruses are classified into types A, B, and C; types A and B cause most human infections. Influenza A is the most common type of influenza virus in humans and is generally responsible for seasonal flu epidemics and, occasionally, pandemics. Influenza A viruses can also infect animals such as birds, pigs, and horses. Infections with influenza B virus are generally restricted to humans and are less frequent causes of epidemics. Influenza A viruses are further divided into subtypes on the basis of 2 surface proteins: hemagglutinin (H) and neuraminidase (N). Seasonal flu is normally caused by subtypes H1, H2, H3, and N1 and N2. In addition to seasonal flu, a novel H1N1 strain was identified in humans in the United States in early 2009.

**Useful For:** Aiding in the diagnosis of influenza infections in conjunction with clinical and epidemiological risk factors

**Interpretation:** Flu A POSITIVE: Flu A target RNA is detected Flu B POSITIVE: Flu B target RNA is detected Flu A and Flu B NEGATIVE: Flu A and Flu B target RNA is not detected Negative results do not preclude influenza virus infection and should not be used as the sole basis for treatment or other patient management decisions.

**Reference Values:**
Negative for Influenza A by nucleic acid amplification
Negative for Influenza B by nucleic acid amplification

**Clinical References:**

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**Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Nasopharyngeal Swab**

**Clinical Information:** Influenza, otherwise known as the “flu,” is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years. Influenza infection may be treated with supportive therapy, as well as...
antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults.(2) RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA.(3-4) Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

**Useful For:** Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test for nasopharyngeal swab specimens

**Interpretation:** A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

**Reference Values:**
Negative

**Clinical References:**

**FLUMS 62668**

**Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Varies**

**Clinical Information:** Influenza, otherwise known as the “flu,” is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, older individuals, patients who are immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year.(1) In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years.(1) Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA).
These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults. RSV and influenza virus RNA can be detected by polymerase chain reaction (PCR) in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA. Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

**Useful For:** Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test. This test should not be performed unless the patient meets clinical and epidemiologic criteria for testing.

**Interpretation:** A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

**Reference Values:**
Negative

**Clinical References:**

**INHAB**

**Inhibin A and B, Tumor Marker, Serum**

**Clinical Information:** Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in the female and Sertoli cells of the testis in the male. They selectively suppress the secretion of pituitary follicle stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum: whereas inhibin B is predominantly produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. Inhibin A is low in the early follicular phase and rises at ovulation to maximum levels in the midluteal phase. In contrast, inhibin B levels increase early in the follicular phase to reach a peak coincident with the onset of the midfollicular phase decline in FSH levels. Inhibin B levels decrease in the late follicular phase. There is a short-lived peak of the hormone 2 days after the midcycle luteinizing hormone (LH) peak. Inhibin B levels remain low during the luteal phase of the cycle. The timing of the inhibin B rise suggests that it plays a role in regulation of folliculogenesis via a negative feedback on the production of FSH. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial (80%), germ cell tumors (10%-15%), and stromal sex-cord tumors (5%-10%). Epithelial ovarian tumors are further subdivided into: serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex cord tumors. Elevations of serum inhibin A and B are detected in some patients with granulosa cell tumors. Inhibin A elevations have been reported in approximately...
70% of granulosa cell tumors. In these patients, inhibin A levels tend to show a 6-fold to 7-fold increase over the reference range value. Inhibin B elevations have been reported in 89% to 100% of patients with granulosa cell tumors. In those patients, inhibin B levels tend to be elevated about 60-fold over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin A and B also appear to be a suitable serum markers for epithelial tumors of the mucinous type with about 20% of cases having elevated inhibin A levels and 55% to 60% of cases having elevated inhibin B levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be a complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels for both proteins are normally very low. Inhibin levels vary in relation to the menstrual cycle and, therefore, are difficult to interpret in premenopausal women. Inhibin B has also been used as a marker of ovarian reserve. Every female is born with a specific number of follicles containing oocytes, a number that steadily and naturally declines with age. The number of follicles remaining in the ovary at any time is called the ovarian reserve. As ovarian reserve diminishes, it is increasingly more difficult for the hormones used for in vitro fertilization (IVF) to stimulate follicle development and, thus, the likelihood of successful oocyte retrieval, fertilization, and embryo transfer decreases, all leading to a lower chance of conceiving. As part of an infertility evaluation, attempts are made to estimate a woman's ovarian reserve. Tests to assess ovarian reserve include: day 3 FSH, day 3 inhibin B, and antimullerian hormone levels. The amount of inhibin B measured in serum during the early follicular phase of the menstrual cycle (day 3) directly reflects the number of follicles in the ovary. Therefore, the higher the inhibin B, the more ovarian follicles present. The level of inhibin B that predicts a poor response to IVF treatment has not been established with this assay. In males, inhibin B levels are higher in men with apparently normal fertility than in those with infertility and abnormal spermatogenesis. Serum inhibin B, when used in combination with FSH, is a more sensitive marker of spermatogenesis than FSH alone. However, the optimal level of inhibin B to assess male infertility has not been established.

Useful For: Aiding in the diagnosis of granulosa cell tumors and mucinous epithelial ovarian tumors Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to secrete inhibit A or overexpress inhibit B

Interpretation: Inhibin A levels are elevated in approximately 70% of patients with granulosa cell tumors and in approximately 20% of patients with epithelial ovarian tumors. Inhibin B levels are elevated in approximately 89% to 100% of patients with granulosa cell tumors and in approximately 55% to 60% of patients with epithelial ovarian tumors. A normal inhibin A or B level does not rule out a mucinous or granulosa ovarian cell tumor. For monitoring of patients with known ovarian cancer, inhibin A and B levels decrease shortly after surgery. Elevations of inhibin A or B after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin A or B elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin A and B. For infertility evaluation, an inhibin B level in the postmenopausal range is suggestive of a diminished or depleted ovarian reserve.

Reference Values:
INHIBIN A, TUMOR MARKER
Males: <2.0 pg/mL
Females
<11 years: <4.7 pg/mL
11-17 years: <97.5 pg/mL
Premenopausal: <97.5 pg/mL
Postmenopausal: <2.1 pg/mL

INHIBIN B
Males
0-23 months: <430 pg/mL
2-4 years: <269 pg/mL
5-7 years: <184 pg/mL
INHA
81049


INHA A, Tumor Marker, Serum

Clinical Information: Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in the female and Sertoli cells of the testis in the male. They selectively suppress the secretion of pituitary follicle stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum: whereas inhibin B is predominantly produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial, stromal sex cord, and germ cell tumors. Epithelial ovarian tumors account for 90% of cases and are further subdivided into: serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex cord tumors, which account for 2% to 5% of all ovarian tumors. Elevations of serum inhibin A and B are detected in some patients with granulosa cell tumors. Inhibin A elevations have been reported in approximately 70% of granulosa cell tumors. In these patients, inhibin A levels tend to show a 6-fold to 7-fold increase over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin A also appears to be suitable markers for epithelial tumors of the mucinous type with about 20% of cases having elevated inhibin A levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be a complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels for both proteins are normally very low. Inhibin A has limited utility as an ovarian cancer marker in premenopausal women, where circulating levels are higher and fluctuate throughout
the menstrual cycle and, therefore, are difficult to interpret.

**Useful For:** Aiding in the diagnosis of patients with granulosa cell tumors of the ovary when used in combination with inhibin B Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to secrete inhibin A

**Interpretation:** Inhibin A levels are elevated in approximately 70% of patients with granulosa cell tumors and in approximately 20% of patients with epithelial ovarian tumors. A normal inhibin A level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin B in these cases might be informative as a higher proportion of mucinous or granulosa ovarian cell tumors will have an elevated inhibin B level. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin A levels decrease shortly after surgery. Elevations of inhibin A after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin A elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin A.

**Reference Values:**
Males: <2.0 pg/mL
Females
  - <11 years: <4.7 pg/mL
  - 11-17 years: <97.5 pg/mL
  - Premenopausal: <97.5 pg/mL
  - Postmenopausal: <2.1 pg/mL

**Clinical References:**

**INHB**

**Inhibin B, Serum**

**Clinical Information:** Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in females and Sertoli cells of the testis in males. Inhibins selectively suppress the secretion of pituitary follicle-stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum, whereas inhibin B is primarily produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. Inhibin A is low in the early follicular phase and rises at ovulation to maximum levels in the mid-luteal phase. In contrast, inhibin B levels increase early in the follicular phase to reach a peak coincident with the onset of the mid-follicular phase decline in FSH levels. Inhibin B levels decrease in the late follicular phase. There is a short-lived peak of the hormone 2 days after the midcycle luteinizing hormone (LH) peak. Inhibin B levels remain low during the luteal phase of the cycle. The timing of the inhibin B rise suggests that it plays a role in regulation of folliculogenesis via a negative feedback on the production of FSH. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial (80%), germ cell tumors (10%-15%), and stromal sex-cord tumors (5%-10%). Epithelial ovarian tumors are further subdivided into serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex-cord tumors. Elevations of serum inhibin A and/or B are detected in some patients with...
granulosa cell tumors. Inhibin B elevations have been reported in 89% to 100% of patients with granulosa cell tumors. In those patients, inhibin B levels tend to be elevated about 60-fold over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin B also appears to be a suitable serum marker for epithelial tumors of the mucinous type with about 55% to 60% having elevated inhibin B levels. In contrast, inhibin is not a very good marker in non-mucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of non-mucinous epithelial ovarian cancer cases. Inhibin seems to be complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels of inhibin are normally very low. Inhibin levels vary in relation to the menstrual cycle and, therefore, are difficult to interpret in premenopausal women. Inhibin B has also been used as a marker of ovarian reserve. Every female is born with a specific number of follicles containing oocytes, a number that steadily and naturally declines with age. The number of follicles remaining in the ovary at any time is called the ovarian reserve. As ovarian reserve diminishes, it is increasingly more difficult for the hormones used for in vitro fertilization (IVF) to stimulate follicle development and, thus, the likelihood of successful oocyte retrieval, fertilization, and embryo transfer decreases, all leading to a lower chance of conceiving. As part of an infertility evaluation, attempts are made to estimate a woman's ovarian reserve. Tests to assess ovarian reserve include: day 3 FSH, day 3 inhibin B, and antimullerian hormone levels. The amount of inhibin B measured in serum during the early follicular phase of the menstrual cycle (day 3) directly reflects the number of follicles in the ovary. Therefore, the higher the inhibin B, the more ovarian follicles present. The level of inhibin B that predicts a poor response to IVF treatment has not been established with this assay. In males, inhibin B levels are higher in men with apparently normal fertility than in those with infertility and abnormal spermatogenesis. Serum inhibin B, when used in combination with FSH, is a more sensitive marker of spermatogenesis than FSH alone. However, the optimal level of inhibin B to assess male infertility has not been established.

**Useful For:** Aiding in the diagnosis of granulosa cell tumors and mucinous epithelial ovarian tumors Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to overexpress inhibin B As an adjunct to follicle-stimulating hormone testing during infertility evaluation

**Interpretation:** Inhibin B levels are elevated in approximately 89% to 100% of patients with granulosa cell tumors and in approximately 55% to 60% of patients with epithelial ovarian tumors. A normal inhibin B level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin A in these cases might be informative. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin B levels decrease to very low or undetectable levels shortly after surgery. Elevations of inhibin B after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin B elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin B. For infertility evaluation, an inhibin B level in the postmenopausal range is suggestive of a diminished or depleted ovarian reserve.

**Reference Values:**

**Males**
- 0-23 months: <430 pg/mL
- 2-4 years: <269 pg/mL
- 5-7 years: <184 pg/mL
- 8-10 years: <214 pg/mL
- 11-13 years: <276 pg/mL
- 14-17 years: <273 pg/mL
- Adults: <399 pg/mL

**Females**
- 0-23 months: <111 pg/mL
- 2-4 years: <44 pg/mL
- 5-7 years: <27 pg/mL
- 8-10 years: <67 pg/mL
- 11-13 years: <120 pg/mL

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
14-17 years: <136 pg/mL
Premenopausal
Follicular: <139 pg/mL
Luteal: <92 pg/mL
Postmenopausal: <10 pg/mL


**INHIB**

**Inhibin Immunostain, Technical Component Only**

**Clinical Information:** Inhibin is a hormone produced by ovarian granulosa and theca cells, and testicular Sertoli and Leydig cells. Inhibin staining can be useful in the diagnosis of sex cord-stromal tumors.

**Useful For:** Identification of sex cord-stromal tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**INHU**

**Insulin (Human), IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to insulin (human)
Difficulties in identifying the allergen responsible for eliciting signs and symptoms
Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Insulin Antibodies, Serum

Clinical Information: The onset of autoimmune diabetes mellitus (type 1 diabetes mellitus) is preceded (and accompanied) by the appearance of autoantibodies to a variety of pancreatic islet cell antigens in serum, including insulin. The level of these autoantibodies is generally low and may even fall during follow-up. In genetically predisposed, but disease-free, individuals (first degree relatives of patients with type 1 diabetes or individuals with permissive HLA alleles), detection of multiple islet cell autoantibodies is a strong predictor for subsequent development of type I diabetes. Once type 1 diabetes has become fully manifest, insulin autoantibody levels usually fall to low or undetectable levels. However, after insulin therapy is initiated, autoantibody production may recur as a memory response. Insulin autoantibody production is more common when therapeutic insulin of animal origin is used (rarely used in contemporary practice). Larger therapeutic doses may be required because of antibody-induced insulin resistance. Insulin antibodies may be found in nondiabetic individuals complaining of hypoglycemic attacks. In this setting their presence can be an indicator of "factitious hypoglycemia" due to the surreptitious injection of insulin, rather than to a clinical problem (eg, insulinoma). However, insulin autoantibodies in nondiabetic subjects can occasionally develop without exposure to exogenous insulin and may rarely become a cause of episodic hypoglycemia. Anti-idiotypic autoantibodies against insulin autoantibodies have been demonstrated in some cases. Interaction of these antibodies with insulin autoantibodies could displace bound insulin from the insulin autoantibodies, resulting in hypoglycemia. In addition to IgG and IgM insulin autoantibodies, IgE antibodies (identified by the fluorescence enzyme immunoassay) may occur. IgE insulin autoantibodies result in immediate hypersensitivity reactions, such as urticaria, but do not lead to insulin resistance or hypoglycemia as can be seen with the IgG antibodies. This test only determines the presence of IgG and IgM antibodies, not IgE antibodies. In conjunction with family history, HLA-typing and measurement of other islet cell autoantibodies (glutamic acid decarboxylase [GAD65] antibody and islet cell antigen
2 antibody [IA-2]), insulin autoantibody testing helps predict the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults. Inclusion of a recently described fourth autoantibody (zinc transporter 8, ZnT8) further enhances the prediction of type 1 diabetes occurrence and its distinction from type 2 diabetes.

**Useful For:** Predicting the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults, when used in conjunction with family history, HLA-typing, and other autoantibodies, including GD65S/81596 Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum and islet cell antigen 2 (IA-2) antibodies Differential diagnosis of type 1 versus type 2 diabetes Evaluating diabetics with insulin resistance in patients with established diabetes (type 1 or type 2) Investigation of hypoglycemia in nondiabetic subjects

**Interpretation:** Seropositivity (> or =0.03 nmol/L) in a patient never treated with insulin is consistent with predisposition to type 1 diabetes. Seropositivity is not as informative of type 2 diabetes status as other islet cell antibodies in patients who are receiving (or have received) insulin therapy because this antibody can arise secondary to therapy. It is thought that high levels of insulin autoantibodies might contribute to insulin resistance. A family history of type 1 diabetes, other organ-specific autoimmunity and a diabetes-permissive HLA phenotype strengthens the prediction of type 1 diabetes development. The detection of multiple islet cell antibodies is indicative of the likely development of future type 1 diabetes. In patients presenting with hypoglycemia, the presence of insulin autoantibodies may indicate surreptitious insulin administration or, rarely, insulin autoantibody-related hypoglycemia. The differential diagnosis cannot be made on the basis of insulin autoantibody detection alone. C-peptide and insulin measurements are always required in addition to insulin autoantibody measurements in the diagnosis of hypoglycemia.

**Reference Values:**
< or =0.02 nmol/L
Reference values apply to all ages.

**Clinical References:**

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**INSUL 70478**

**Insulin Immunostain, Technical Component Only**

**Clinical Information:** Insulin is a polypeptide hormone secreted by the beta cells of the islets of Langerhans in the pancreas. It promotes glycogen storage, formation of triglycerides, and synthesis of protein and nucleic acids. Cytoplasmic staining is seen in normal pancreatic islet beta cells and insulin secreting islet cell tumors.

**Useful For:** Identification of normal pancreatic islet beta cells and insulin secreting islet cell tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Insulin, Free and Total, Serum**

**Clinical Information:** Insulin is produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Circulating insulin antibodies develop after diabetic patients are treated with exogenous insulin preparations. The presence of insulin antibodies has 2 main consequences: 1. Insulin antibodies will directly bind to insulin, making it unavailable for metabolic activity. 2. Insulin antibodies may adversely affect the binding characteristics of insulin in immunoassays, making reliable quantitation difficult. Free (bioactive) insulin could be measured after polyethylene glycol (PEG) precipitation of insulin antibodies and their bound insulin. If insulin antibodies are not present, the free and total insulin should be equivalent. The laboratory will report results of the total insulin (without PEG precipitation) and the free insulin (with PEG precipitation).

**Useful For:** Assessing free (bioactive) insulin concentrations in patients with known or suspected insulin antibodies

**Interpretation:** If insulin antibodies are not present, the free and total insulin should be equivalent. A significant difference between total and free insulin is suggestive of the presence of insulin antibodies. During prolonged fasting, when the patient's glucose is reduced to less than 40.0 mg/dL, elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. In patients with insulin-dependent diabetes mellitus, insulin levels generally decline. In the early stage of noninsulin-dependent diabetes mellitus (NIDDM), insulin levels are either normal or elevated. In the late stage of NIDDM, insulin levels may also decline as levels of proinsulin decrease.

**Reference Values:**

- **FREE INSULIN**
  
  2.6-24.9 mcIU/mL

- **TOTAL INSULIN**
  
  2.6-24.9 mcIU/mL


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**Insulin, Serum**

**Clinical Information:** Insulin is a hormone produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Type 1 diabetes (insulin-dependent diabetes) is caused by insulin deficiency due to destruction of insulin-producing pancreatic islet (beta) cells. Type 2 diabetes (noninsulin-dependent diabetes) is characterized by resistance to the action of insulin (insulin resistance). Insulin levels may be increased in patients with pancreatic beta cell tumors (insulinoma).

**Useful For:** Diagnosing insulinoma, when used in conjunction with proinsulin and C-peptide measurements Management of diabetes mellitus

**Interpretation:** During prolonged fasting, when the patient's glucose level is reduced to <40 mg/dL, an elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. Insulin levels generally decline in patients with type 1 diabetes mellitus. In the early stage of type 2 diabetes, insulin levels are either normal or elevated. In the late stage of type 2 diabetes, insulin levels decline. In normal individuals, insulin levels parallel blood glucose levels. To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio): -Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L. -Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L.
Reference Values:
2.6-24.9 mcIU/mL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References:

Insulin-Like Growth Factor 1 and Insulin-Like Growth Factor-Binding Protein 3 Growth Panel, Serum

Clinical Information: Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight 7.6 kDa). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, but the liver is the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular insulin-like growth factor-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. IGFBP3 is a 264-amino acid peptide (MW 29kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport, and control bioavailability and half-life of IGFs, in particular IGF1, the major mediator of the anabolic- and growth-promoting effects of GH. In addition to its IGF binding-function, IGFBP3 also exhibits intrinsic growth-regulating effects that are not yet fully understood, but have evoked interest with regards to a possible role of IGFBP3 as a prognostic tumor marker. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious mutations in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast,colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate nutrition.

Useful For: Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment Insulin-like growth factor binding protein 3 can be used as a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism.
**Interpretation:** Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity, and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little if anything to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (Standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

**Reference Values:**

**INSULIN-LIKE GROWTH FACTOR 1**

Males:
- 0-11 months: 18-156 ng/mL
- 1 year: 14-203 ng/mL
- 2 years: 16-222 ng/mL
- 3 years: 22-229 ng/mL
- 4 years: 30-236 ng/mL
- 5 years: 39-250 ng/mL
- 6 years: 47-275 ng/mL
- 7 years: 54-312 ng/mL
- 8 years: 61-356 ng/mL
- 9 years: 67-405 ng/mL
- 10 years: 73-456 ng/mL
- 11 years: 79-506 ng/mL
- 12 years: 84-551 ng/mL
- 13 years: 90-589 ng/mL
- 14 years: 95-618 ng/mL
- 15 years: 99-633 ng/mL
- 16 years: 104-633 ng/mL
- 17 years: 107-615 ng/mL
- 18-22 years: 91-442 ng/mL
- 23-25 years: 66-346 ng/mL
- 26-30 years: 60-329 ng/mL
- 31-35 years: 54-310 ng/mL
- 36-40 years: 48-292 ng/mL
- 41-45 years: 44-275 ng/mL
- 46-50 years: 40-259 ng/mL
- 51-55 years: 37-245 ng/mL
- 56-60 years: 34-232 ng/mL
61-65 years: 33-220 ng/mL
66-70 years: 32-209 ng/mL
71-75 years: 32-200 ng/mL
76-80 years: 33-192 ng/mL
81-85 years: 33-185 ng/mL
86-90 years: 33-179 ng/mL
> or =91 years: 32-173 ng/mL

Females:
0-11 months: 14-192 ng/mL
1 year: 23-243 ng/mL
2 years: 28-256 ng/mL
3 years: 31-249 ng/mL
4 years: 33-237 ng/mL
5 years: 36-234 ng/mL
6 years: 39-246 ng/mL
7 years: 44-279 ng/mL
8 years: 51-334 ng/mL
9 years: 61-408 ng/mL
10 years: 73-495 ng/mL
11 years: 88-585 ng/mL
12 years: 104-665 ng/mL
13 years: 120-719 ng/mL
14 years: 136-729 ng/mL
15 years: 147-691 ng/mL
16 years: 153-611 ng/mL
17 years: 149-509 ng/mL
18-22 years: 85-370 ng/mL
23-25 years: 73-320 ng/mL
26-30 years: 66-303 ng/mL
31-35 years: 59-279 ng/mL
36-40 years: 54-258 ng/mL
41-45 years: 49-240 ng/mL
46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:
Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL

Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 3

1-7 days: < or =0.7 mcg/mL
8-14 days: 0.5-1.4 mcg/mL
15 days-11 months: unavailable
1 year: 0.7-3.6 mcg/mL
2 years: 0.8-3.9 mcg/mL
3 years: 0.9-4.3 mcg/mL
4 years: 1.0-4.7 mcg/mL
5 years: 1.1-5.2 mcg/mL
6 years: 1.3-5.6 mcg/mL
7 years: 1.4-6.1 mcg/mL
8 years: 1.6-6.5 mcg/mL
9 years: 1.8-7.1 mcg/mL
10 years: 2.1-7.7 mcg/mL
11 years: 2.4-8.4 mcg/mL
12 years: 2.7-8.9 mcg/mL
13 years: 3.1-9.5 mcg/mL
14 years: 3.3-10 mcg/mL
15 years: 3.5-10 mcg/mL
16 years: 3.4-9.5 mcg/mL
17 years: 3.2-8.7 mcg/mL
18 years: 3.1-7.9 mcg/mL
19 years: 2.9-7.3 mcg/mL
20 years: 2.9-7.2 mcg/mL
21-25 years: 3.4-7.8 mcg/mL
26-30 years: 3.5-7.6 mcg/mL
31-35 years: 3.5-7.0 mcg/mL
36-40 years: 3.4-6.7 mcg/mL
41-45 years: 3.3-6.6 mcg/mL
46-50 years: 3.3-6.7 mcg/mL
51-55 years: 3.4-6.8 mcg/mL
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:
Males
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL
Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL
Females
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.8-6.9 mcg/mL
Stage III: 3.9-9.4 mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.7-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage 1 (prepubertal) to Tanner stage 2 (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage 5 (young adult) should be reached by age 18.

Clinical References:

Insulin-like Growth Factor 2 (IGF-2)

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Range (ng/mL)</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Prepubertal</td>
<td>258–882</td>
<td>570</td>
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<tr>
<td>Pubertal</td>
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<tr>
<td>Adults</td>
<td>333–967</td>
<td>650</td>
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</table>

Insulin-Like Growth Factor-1, Mass Spectrometry, Serum

Clinical Information: Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight 7649 Da; Uniprot Accession P05019 [aa 49-118]). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, but the liver is the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular insulin-like growth factor-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. Noncomplexed IGF1 and IGFBP3 have short half-lives (1/2 of 10 and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated
measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH
deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood
GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones.
Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation
or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is
mild-to-moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure).
These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH
resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or
deleterious mutations in IGFBP3, its binding proteins, or its receptor signaling cascades. Both GH deficiency
and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while
severe resistance will usually not respond to GH. However, such patients might respond to recombinant
IGF1 therapy, unless the underlying defect is in the IGFBP3 receptor or its downstream signaling systems.
The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen
mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased
cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum
IGF1 and IGFBP3 levels often indicate a sustained overproduction of GH, or excessive rhGH therapy.
Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if
acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with
generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression
neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is
plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes.
Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate
nutrition.

Useful For:
- Evaluation of growth disorders
- Evaluation of growth hormone deficiency or excess in children and adults
- Monitoring of recombinant human growth hormone treatment
- Follow-up of individuals with acromegaly and gigantism

Interpretation:
Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity, and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little if anything to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (Standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be
within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

Reference Values:
Males:
- 0-11 months: 18-156 ng/mL
- 1 year: 14-203 ng/mL
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Females:

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<td>54-258</td>
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<td>41-45 years</td>
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46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:
Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL


Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 +/- 2 years and for girls at a median age of 10.5 +/- 2 years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References:
that transport, control bioavailability and half-life of the insulin-like growth factors (IGF), in particular IGF-1, the major mediator of the anabolic- and growth-promoting effects of growth hormone (GH). Noncomplexed IGFBP-3 and IGF-1 have short half-lives (t1/2) of 30 to 90 minutes and 10 minutes, respectively, while the IGFBP-3/IGF-1 complex is cleared with a much slower t1/2 of 12 hours. In addition to its IGF-binding function, IGFBP-3 also exhibits intrinsic growth-regulating effects that are not yet fully understood but have evoked interest with regards to a possible role of IGFBP-3 as a prognostic tumor marker. The secretion patterns of IGFBP-3 and IGF-1 mimic each other; their respective syntheses are primarily controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGFBP-3 and IGF-1 levels show only minor fluctuations. IGFBP-3 and IGF-1 serum levels therefore represent a stable and integrated measurement of GH production and tissue effect. Low IGFBP-3 and IGF-1 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF-1 and IGFBP-3 levels within the reference range. Severe childhood GH resistance is rare and usually due to GH-receptor defects. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections. The prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGFBP-3 and IGF-1 levels indicate a sustained overproduction of GH or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk, and diminished longevity. It is plausible, but unproven, that long-term rhGH-overtreatment may result in similar adverse outcomes.

**Useful For:** Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment As a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism

**Interpretation:** For all applications, insulin-like growth factor 1 (IGF-1) measurement has generally been shown to have superior diagnostic sensitivity and specificity compared with insulin-like growth factor-binding protein 3 (IGFBP-3). IGFBP-3 testing should, therefore, usually be combined with IGF-1 testing. The combination of IGF-1 and IGFBP-3 measurements appears superior to determining either analyte alone in the diagnosis of growth hormone (GH) deficiency and resistance, and in the monitoring of recombinant human GH therapy. By contrast, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP-3 measurement adds little if anything to IGF-1 testing. IGF-1 and IGFBP-3 levels below the 2.5th percentile for age are consistent with GH deficiency or severe resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels are also low and show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels are substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of an endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF-1 and IGFBP-3 levels within the reference range, ideally within the middle to upper third. Higher levels are rarely associated with any further therapeutic gains but could potentially lead to long-term problems of GH excess. Elevated IGF-1 and IGFBP-3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF-1 levels correlate better with clinical disease activity than IGFBP-3 levels.

**Reference Values:**
- 1-7 days: ≤ 0.7 mcg/mL
- 8-14 days: 0.5-1.4 mcg/mL
- 15 days-11 months: unavailable

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 1456
<table>
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<th>Age Group</th>
<th>Range</th>
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<tr>
<td>81-85 years</td>
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Tanner Stages:

**Males**
- Stage I: 1.4-5.2 mcg/mL
- Stage II: 2.3-6.3 mcg/mL
- Stage III: 3.1-8.9 mcg/mL
- Stage IV: 3.7-8.7 mcg/mL
- Stage V: 2.6-8.6 mcg/mL

**Females**
- Stage I: 1.2-6.4 mcg/mL
- Stage II: 2.8-6.9 mcg/mL
- Stage III: 3.9-9.4 mcg/mL
- Stage IV: 3.3-8.1 mcg/mL
- Stage V: 2.7-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage I (prepubertal) to Tanner stage II (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in girls who are obese and in African American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

**Clinical References:** 1. Boscato LM, Stuart MC: Heterophilic antibodies: a problem for all

**FGBP1**

**Insulin-like Growth Factor-binding Protein-1 (IGFBP-1)**

**Useful For:** Identify women who are at high risk for developing preeclampsia.

**Reference Values:**

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<th>Age</th>
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<td>10-150</td>
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</table>

**INSM1**

**Insulinoma-Associated Protein 1 (INSM1), Immunostain, Technical Component Only**

**Clinical Information:** Insulinoma associated protein 1 (INSM1) is expressed in tissues with neuroendocrine differentiation. INSMA1 is a sensitive and specific marker for neuroendocrine tumors.

**Useful For:** Identification of neuroendocrine tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Intact Fibroblast Growth Factor 23, Serum

Clinical Information: Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate (phosphorus) homeostasis. FGF23 is secreted primarily by bone, followed by thymus, heart, brain and, in low levels, by several other tissues. High serum phosphate (phosphorus) concentrations stimulate FGF23 expression and secretion through a yet poorly understood mechanism. Only intact FGF23 is considered bioactive. Intact FGF23 interacts with a specific receptor on renal tubular cells, decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased phosphate reabsorption. In addition, gene transcription of 1-alpha-hydroxylase is downregulated, reducing bioactive 1,25-dihydroxy vitamin D, thereby further decreasing phosphate reabsorption. Eventually, falling serum phosphate concentrations lead to diminished FGF23 secretion, closing the feedback loop. Measurement of FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism in patients with either normal or impaired renal function. When FGF23 levels are pathologically elevated in individuals with normal renal function, hypophosphatemia, with or without osteomalacia, ensues. This can occur in rare, usually benign, mixed connective tissue tumors that contain characteristic complex vascular structures, osteoclast-like giant cells, cartilaginous elements, and dystrophic calcifications. These neoplasms secrete FGF23 ectopically and autonomously (tumor-induced osteomalacia; TIO). In less than one-fourth of cases, a different benign or malignant soft tissue tumor type or, extremely rarely, a carcinoma, may be the cause of paraneoplastic FGF23 secretion. In either scenario, complete removal of the tumor cures the TIO. Hypophosphatemia and skeletal abnormalities are also observed in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR). In XLH, variants in the PHEX (phosphate-regulating neutral endopeptidase) gene, which encodes a cell-surface-bound protein-cleavage enzyme, affect bioactive FGF23 secretion.

Although the pathogenesis of XLH is not fully understood, animal studies indicate that loss of PHEX function results in enhanced secretion of FGF23. In ADHR, FGF23 variants render the protein resistant to proteolytic cleavage, thereby increasing FGF23 levels. However, not all FGF23 variants increase renal phosphate secretions. Variants that impair FGF23 signaling, rather than increase its protease resistance, are associated with the syndrome of familial tumoral calcinosis (ectopic calcifications) with hyperphosphatemia. In patients with renal failure, FGF23 contributes to renal osteodystrophy. The patient’s kidneys can no longer excrete sufficient amounts of phosphate. This leads to marked increases in FGF23 secretion as a compensatory response, aggravating the 1,25-dihydroxy vitamin D deficiency of renal failure and the consequent secondary hyperparathyroidism. In circulation, intact FGF-23 is cleaved to generate two biologically inactive fragments, a N-terminal fragment and a C-terminal fragment. FGF23 has a rapid clearance and short half-life which ranges between 46 and 58 min for intact and C-terminal fragments, respectively. Different types of FGF-23 immunoassays are available, those targeting the intact form (iFGF23), and those detecting C-terminal fragments (cFGF23). Various studies have suggested that iFGF23 assays are more sensitive than cFGF23 for the detection of FGF23 concentrations in patients with TIO and patients with XLH. In addition, iFGF23 concentrations are not affected by iron deficiency which may lead to false positive results when using cFGF23 assays.

Useful For: Diagnosing and monitoring tumor induced osteomalacia Diagnosing X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets Diagnosing familial tumoral calcinosis with hyperphosphatemia

Interpretation: Increased fibroblast growth factor 23 (FGF23) concentrations are present in individuals with renal phosphate-wasting diseases such as autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR), X-linked hypophosphatemia rickets (XLH) and tumor induced osteomalacia (TIO). Clinically, FGF23 measurement is useful in the differential diagnosis of these hypophosphatemic diseases since the patient presents with high FGF23 levels along with hypophosphatemia. In other causes of hypophosphatemia, such as vitamin D deficiency, FGF23 levels are low. In FGF23-producing tumors, a decrease in FGF23 concentrations following surgery is a reliable indication of complete tumor resection. Intact FGF23 concentrations are elevated in patients with TIO or XLH. A study detected elevations of intact FGF23 in 19 of 22 TIO cases (86%).(1) In XLH, elevations of intact FGF23 were observed in 88% of patients (9 of 10 children and 13 of 15 adults).(2) While levels of intact FGF23 in XLH are usually elevated, FGF23 concentrations within the reference interval do not exclude the disease and should be interpreted in the setting of phosphate concentrations (ie, an FGF23 concentration in the upper level of the reference interval in the context of hypophosphatemia might be indicative of XLH). In ADHR, FGF23 concentrations are not consistently elevated, and the severity of renal phosphate-wasting may wax and
wane; FGF23 concentrations are normal during quiescent periods when serum phosphate levels are normal, and they are elevated during active, hypophosphatemic phases of the disease.(3) FGF23 concentrations are influenced by factors such as phosphate intake and vitamin D therapy. Therefore, intact FGF23 levels are most informative in untreated patients.

**Reference Values:**

- Pediatric (<18 yrs): < or = 52 pg/mL
- Adults (> or = 18 yrs): < or = 59 pg/mL

**Clinical References:**


**Integrase Interactor 1 (INI1/BAF47) Immunostain, Technical Component Only**

**Clinical Information:** Integrase interactor 1 (INI1) is a member of the SWI/SNF (SWItch/sucrose non-fermentable) chromatin remodeling complex. They play an important role in regulation of transcription by modulating access of protein to DNA. Loss of function of these complexes has been implicated in human cancers. Point alterations and deletions of the INI BAF47 gene may be seen in pediatric rhabdoid tumors, Rhabdomyosarcoma, chronic myeloid leukemia, and in central nervous system (CNS) tumors (medulloblastomas and choroid plexus carcinomas) where loss of nuclear staining for INI1/BAF47 is seen. In normal tissues, nuclear expression of INI1/BAF4 in should be present in all cell types.

**Useful For:** Part of a panel of immunostains where loss of staining can be used as a marker of various neoplasms

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


**Interference Evaluation Heterophile, Beta-Human Chorionic Gonadotropin, Serum**

**Clinical Information:** Some patients, due to exposure to animal antigens, have developed antibodies that interfere with immunoassay testing. These heterophilic antibodies are able to bind to animal
antibodies used in immunoassays. It has been found that a significant percentage of certain sandwich immunoassay results are false-positive results caused by heterophilic antibody interference. The most commonly reported assay interference effect of heterophilic antibodies is a false-positive assay result. False-negative assay results have also been reported in the literature. Manufacturers add blocking agents to their reagents, but occasional patient samples containing heterophile antibodies are incompletely blocked. Subsequent reporting of erroneous results can have adverse effects on patient management, especially with tumor marker assays. Among immunometric assays, human chorionic gonadotropin (hCG) assays have been found uniquely susceptible to heterophile antibody interference, resulting in occasional false-positive results. The current assay has proven robust in this respect, but rare interferences still occur. Typically, the observed false-positive elevations are modest, ranging from just above the reference range to levels of 50 to 60 IU/L. If such results are seen and are discordant with the clinical picture, or other biochemical or imaging tests, then the laboratory should be alerted. Repeat analysis of the specimen in question, after additional blocking treatment, may resolve the issue. Dilution of the specimen prior to assay performance often yields unexpected non-linear results in the presence of interfering substances such as heterophile antibodies. Heterophile blocking tube (HBT) treatment is used for troubleshooting samples that yield results that are either non-linear or do not match the clinical picture of the patient and are suspected of containing heterophile antibodies. Finally, assessment of an analyte such as hCG with an alternative assay will often lead to apparent discrepant results in the presence of a heterophile antibody, as heterophile antibodies often interact differently with alternative assay antibodies. Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight [MW] approximately 36,000 Da) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyrotropin (TSH). The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da; glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans), it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. HCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in particular seminomatous and nonseminomatous testicular tumors; ovarian germ cell tumors; gestational trophoblastic disease (GTD: hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including the electrochemiluminescent immunoassay© assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours, and eventually return to the reference range. The alternate testing method is an enzymatic immunoassay. Values obtained with different assay methods or kits may be different and cannot be used interchangeably.

**Useful For:** Evaluation of suspected interference from heterophile antibodies causing a falsely elevated human chorionic gonadotropin (hCG) result. This test is not to be used for pregnancy testing.

**Interpretation:** Specimens are evaluated for potential heterophile antibody interference in the Roche Elecsys total beta-human chorionic gonadotropin (hCG) immunoassay. Evaluation consists of pretreatment with commercial heterophile antibody blocking tube reagents, serial dilution of the sample, and testing on an alternate platform (Beckman Coulter DxI). The presence of heterophile antibody interference in the Roche Elecsys assay is not suspected when the results from the pretreatment, serial dilution, and the alternative platform agree within 20% of the original result. The presence of heterophile antibody interference in the Roche Elecsys assay is suspected when 1 or more of the following are observed: a significant decrease in hCG (>20%) upon treatment of the sample with the patient and are suspected of containing heterophile antibodies. Finally, assessment of an analyte such as hCG with an alternative assay will often lead to apparent discrepant results in the presence of a heterophile antibody, as heterophile antibodies often interact differently with alternative assay antibodies. Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight [MW] approximately 36,000 Da) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyrotropin (TSH). The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da; glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans), it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. HCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in particular seminomatous and nonseminomatous testicular tumors; ovarian germ cell tumors; gestational trophoblastic disease (GTD: hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including the electrochemiluminescent immunoassay© assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours, and eventually return to the reference range. The alternate testing method is an enzymatic immunoassay. Values obtained with different assay methods or kits may be different and cannot be used interchangeably.

**Useful For:** Evaluation of suspected interference from heterophile antibodies causing a falsely elevated human chorionic gonadotropin (hCG) result. This test is not to be used for pregnancy testing.

**Interpretation:** Specimens are evaluated for potential heterophile antibody interference in the Roche Elecsys total beta-human chorionic gonadotropin (hCG) immunoassay. Evaluation consists of pretreatment with commercial heterophile antibody blocking tube reagents, serial dilution of the sample, and testing on an alternate platform (Beckman Coulter DxI). The presence of heterophile antibody interference in the Roche Elecsys assay is not suspected when the results from the pretreatment, serial dilution, and the alternative platform agree within 20% of the original result. The presence of heterophile antibody interference in the Roche Elecsys assay is suspected when 1 or more of the following are observed: a significant decrease in hCG (>20%) upon treatment of the sample with

Useful For: Evaluation of suspected interference from heterophile antibodies causing a falsely elevated human chorionic gonadotropin (hCG) result. This test is not to be used for pregnancy testing.

**Interpretation:** Specimens are evaluated for potential heterophile antibody interference in the Roche Elecsys total beta-human chorionic gonadotropin (hCG) immunoassay. Evaluation consists of pretreatment with commercial heterophile antibody blocking tube reagents, serial dilution of the sample, and testing on an alternate platform (Beckman Coulter DxI). The presence of heterophile antibody interference in the Roche Elecsys assay is not suspected when the results from the pretreatment, serial dilution, and the alternative platform agree within 20% of the original result. The presence of heterophile antibody interference in the Roche Elecsys assay is suspected when 1 or more of the following are observed: a significant decrease in hCG (>20%) upon treatment of the sample with
heterophile antibody blocking reagents, lack of linearity upon serial dilutions, or a significant difference in hCG concentration on the alternate platform. When a heterophile antibody interference affecting the Roche Elecsys assay is suspected, the hCG results from this assay are considered false-positive and should not be used in clinical management. In males, hCG concentrations above the reference interval can occur if the patient is hypogonadal. Inadequate negative feedback to the pituitary, due to low sex hormone levels, may result in elevated hCG. It is recommended that serum luteinizing hormone (LH) or follicle stimulating hormone (FSH) be determined to assess this possibility. Heterophile reagent blocking tubes (HBT-Scantibodies) contain a unique blocking reagent composed of specific binders, which inactivate heterophilic antibodies. Once the specific binders have bound to the heterophilic antibodies, the antibodies are no longer able to cause immunoassay interference. Blocking agents do not inhibit all heterophilic antibodies completely and cannot be used to rule out the presence of heterophile antibody interference. For patients with apparent serum hCG concentrations greater than 15 to 20 IU/L, hCG should also be detectable in urine, if it is truly elevated. Failure to detect urinary hCG in such patients can support the suspicion of a false-positive serum hCG test. After delivery, miscarriage, or pregnancy termination, hCG levels fall with a half-life of 24 to 36 hours, until prepregnancy levels are reached. An absent or significantly slower decline is seen in patients with retained products of conception. Gestational trophoblastic disease (GTD) is associated with very considerable elevations of hCG, usually above 2 multiples of the median for gestational age persisting, or even rising beyond, the first trimester. Serum hCG levels are elevated in approximately 40% to 50% of patients with nonseminomatous testicular cancer and 20% to 40% of patients with seminoma. Markedly elevated levels of hCG (>5000 IU/L) are uncommon in patients with pure seminoma and indicate the presence of a mixed testicular cancer. Ovarian germ cell tumors (approximately 10% of ovarian tumors) display elevated hCG levels in 20% to 50% of cases. Teratomas in children may overproduce hCG, even when benign, resulting in precocious pseudopuberty. Levels may be elevated to similar levels as seen in testicular cancer. Among non-reproductive tumors, hepatobiliary tumors (hepatoblastomas, hepatocellular carcinomas, and cholangiocarcinomas) and neuroendocrine tumors (eg, islet cell tumors and carcinoids) are those most commonly associated with hCG production. Many hCG-producing tumors also produce other embryonic proteins/antigens, in particular alpha fetoprotein (AFP). Therefore, AFP should also be measured in the diagnostic workup of such neoplasms. Complete therapeutic response in hCG-secreting tumors is characterized by a decline in hCG levels with an apparent half-life of 24 to 36 hours and eventual return to concentrations within the reference range. GTD and some tumors may produce hyperglycosylated hCG with a longer half-life, but an apparent half-life of greater than 3 days suggests the presence of residual hCG-producing tumor tissue. A rise in hCG levels above the reference range in patients with hCG-producing tumors that had previously been treated successfully suggests possible local or distant metastatic recurrence.

**Reference Values:**

**BETA-HUMAN CHORIONIC GONADOTROPIN, QUANTITATIVE, SERUM**

**Children (1,2)**

**Males**

- Birth-3 months: < or =50 IU/L*
- >3 months-<18 years: <1.4 IU/L

**Females**

- Birth-3 months: < or =50 IU/L*
- >3 months-<18 years: <1.0 IU/L

Pediatric reference values based on:


*Human chorionic gonadotropin (hCG), produced in the placenta, partially passes the placental barrier. Newborn serum beta-hCG concentrations are approximately 1/400th of the corresponding maternal serum concentrations, resulting in neonate beta-hCG levels of 10-50 IU/L at birth. Clearance half-life is approximately 2-3 days. Therefore, by 3 months of age, levels comparable to adults should be reached.

**Adults (97.5th percentile)**

**Males:** <1.4 IU/L

**Females**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Premenopausal, nonpregnant: <1.0 IU/L  
Postmenopausal: <7.0 IU/L

**HUMAN CHORIONIC GONADOTROPIN, ALTERNATIVE METHOD**

**Males**
Birth-3 months: Not established  
>3 months-49 years: <0.6 IU/L  
50 years-80 years: <1.6 IU/L  
>80 years: Not established

**Females**
Birth-3 months: Not established  
>3 months-40 years: <0.6 IU/L  
41 years-50 years: <6.2 IU/L  
51 years-150 years: <7.8 IU/L


**FIFNY** 57586

**Interferon-gamma (IFN-y) Serum**

**Reference Values:**  
<2.0 pg/mL

**FINA** 91708

**Interleukin 1-Alfa**

**Clinical Information:** The Interleukins belong to the family termed cytokines. They are peptides used by immune and inflammatory cells to communicate and control cell operations. The cytokines have some similar actions to the Growth Factors but Growth Factors regulate proliferation of non-immune cells. Interleukin 1a is a 17,500 molecular weight peptide derived primarily from macrophages, fibroblasts, endothelial cells, and B cells. The major target cells are T and B cells, Fibroblasts, and Hepatocytes. Interleukin 1a shares a receptor with Interleukin 1b although they are significantly different structurally. Interleukin 1a promotes antigen specific immune responses, inflammation, Prostaglandin secretion, Colony Stimulating Factors, proteoglycanase, collagenase, and gelatinase activity, and release of Interleukin 2 from T cells. Levels are stimulated by liposaccharide, endotoxins, inflammatory agents, lectin, Tumor Necrosis Factor, and Interferons. Levels are suppressed by Corticosteroids, Prostaglandin E2, and suppressant lymphocytes.

**Reference Values:**
Less than 3.9 pg/mL


**Interleukin 1-Beta**

**Clinical Information:** The Interleukins belong to the family termed cytokines. They are peptides used by immune and inflammatory cells to communicate and control cell operations. The cytokines have some similar actions to the Growth Factors but Growth Factors regulate proliferation of non-immune cells. Interleukin 1b is a 17,500 molecular weight peptide derived primarily from macrophages, fibroblasts, endothelial cells, and B cells. The major target cells are T and B cells, Fibroblasts, and Hepatocytes and it has pyrogenic activity. Interleukin 1b shares a receptor with Interleukin 1a although they are significantly different structurally. Interleukin 1b promotes antigen specific immune responses, inflammation, secretion, Colony Stimulating Factors, proteoglycanase, collagenase, and gelatinase activity, acute phase response, and cartilage resorption. Interleukin 1b increases accumulation of cell-associated and extracellular arachidonic acid, and induces release of Interleukin 6.

**Reference Values:**
Less than 1.0 pg/mL


**Interleukin 2**

**Interpretation:** Interpretive Information: Cytokines Results are to be used for research purposes or in attempts to understand the pathophysiology of immune, infectious, or inflammatory disorders.

**Reference Values:**
2.1 pg/mL or less

**Interleukin 2 Receptor, Soluble**

**Interpretation:** Interpretive Information: Cytokines Results are used to understand the pathophysiology of immune, infectious, or inflammatory disorders or may be used for research purposes.

**Reference Values:**
175.3 pg/mL - 858.2 pg/mL

**Interleukin 28B (IL28B) Variant (rs12979860), Varies**

**Clinical Information:** Individuals with hepatitis C virus (HCV) genotype 1 infections have variable responses to treatment with pegylated-interferon and ribavirin combination therapy. Some individuals will respond to treatment with sustained viral response, while other patients have poor response and fail to achieve sustained viral clearance. Response to pegylated-interferon and ribavirin combination therapy in HCV genotype 1-infected individuals has been found to be closely associated with a single-nucleotide variant (SNV), designated rs12979860, located 3 kilobases upstream from the interleukin 28B gene locus (IL28B, also known as IFNL3) present on human chromosome 19. HCV genotype 1-infected individuals...
with the CC genotype, as compared to either the CT or TT genotypes, of this SNP in IL28B have approximately 2- to 3-fold greater rates of sustained viral response to combined pegylated-interferon and ribavirin therapy. (1) Similar increases in sustained viral response rates were observed across various racial groups, including European Americans (95% CI, 1.8- to 2.3-fold), African Americans (95% CI, 1.9- to 4.7-fold), and Hispanics (95% CI, 1.4- to 3.2-fold). (1) The CC genotype has also been associated with a 3-fold increase in rate of spontaneous clearance of HCV. (2,4) The SNV in IL28B is only one of many factors that can influence response rates to pegylated-interferon and ribavirin combination therapy in HCV genotype 1 infection, and the SNV genotype result should be interpreted in the context of other clinical factors present in a given patient. Frequency of the rs12979860 C allele varies across different racial and ethnic groups. The rs12979860 C variant is most frequently present in individuals from East Asia (allele frequency >0.9) and least common in individuals of African origin (allele frequency 0.2-0.5). (2) In a recent US-based study, the favorable CC genotype was observed in 37% of whites, 29% Hispanics, and 14% of African Americans tested. The mechanism by which the IL28B genotype mediates response to pegylated-interferon and ribavirin combination therapy among HCV genotype 1-infected individuals is not yet understood and is the subject of intense ongoing research. The impact of the IL28B-related alteration on response rates in patients infected with HCV genotypes other than genotype 1 is still being investigated.

Useful For: Predicting responsiveness of genotype 1 hepatitis C viral infections to combined pegylated-interferon and ribavirin-based therapies

Interpretation: An interpretative report will be provided.

Reference Values: An interpretive report will be provided.


Interleukin 5, Plasma

Clinical Information: Interleukin-5 (IL-5) is a homodimer composed of two 20-kD subunits. (1) It is expressed primarily by CD4+ Th2 (helper T cells, subset 2) cells and, to a lesser extent, by activated mast cells. (2) IL-5 acts on mature eosinophils, leading to proliferation, activation, and differentiation. IL-5 is a critical part of the immune response to helminths. Eosinophils activated by IL-5 will bind, through Fc receptors, to helminths that have been opsonized by IgG or IgA. Elevations in IL-5 may be observed in conditions associated with hypereosinophilia. Hypereosinophilia is most commonly seen in various forms of atopic disease, including urticaria, asthma, allergic bronchopulmonary aspergillosis, and drug allergies. (3) Elevated numbers of eosinophils may also be observed in certain vasculitides, specifically eosinophilic granulomatosis with polyangiitis (EGPA). EGPA is characterized by asthma, pulmonary infiltrates, history of allergies, and hypereosinophilia usually above 1500/mL. Hypereosinophilia may also be observed in certain primary immunodeficiencies (such as Job syndrome), leukemias, and lymphomas. IL-5 is thought to be important in driving eosinophil proliferation in these various conditions. (4) Recently, an advisory committee of the FDA has recommended that mepolizumab, a monoclonal anti-IL-5 antibody, be approved for the treatment of severe eosinophilic asthma in adults. (5) Other IL-5 blocking antibodies (reslizumab and benralizumab) are also in development, with clinical trials designed to determine specific clinical utility.

Useful For: Evaluation of patients with disorders known to be associated with hypereosinophilia

Interpretation: Elevated concentrations of interleukin-5 (IL-5) may indicate an expanded Th2
(helper T cells, subset 2)-immune response, which may be associated with hypereosinophilia.

**Reference Values:**

< or =1.0 pg/mL

**Clinical References:**


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**Interleukin 6, Plasma**

**Clinical Information:** Interleukin-6 (IL-6) has important roles in both innate and adaptive immunity. IL-6 can be produced by a variety of different cell types, including macrophages, endothelial cells, and T cells. This production can be initiated in response to microbial invasion or other cytokines, such as tumor necrosis factor (TNF). As part of the innate immune system, IL-6 acts on hepatocytes to induce expression of C-reactive protein (CRP), fibrinogen, and serum amyloid A, also known as the acute phase response. Within the adaptive immune response, IL-6 plays a key role in activating antibody-producing B cells to proliferate, leading to an enhanced antibody response. Concentrations of IL-6 are elevated in patients with infection, sepsis, and septicemia. In addition, IL-6 concentrations appear to correlate with severity of sepsis, as defined by clinical and laboratory parameters. Elevations in IL-6 also appear to be associated with more localized infections, such as prosthetic joint infections (PJI). A recent meta-analysis demonstrated that IL-6 had improved diagnostic accuracy for PJI compared to CRP, erythrocyte sedimentation rate (ESR), and white blood cell counts. IL-6 is also elevated in numerous chronic inflammatory disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and inflammatory bowel disease (IBD). There is evidence that IL-6 is involved in the pathogenesis of certain chronic inflammatory disorders. Tocilizumab, an antibody that blocks IL-6 function by binding to the IL-6 receptor, has been approved for the treatment of RA. In a randomized trial, 50% to 60% of patients receiving tocilizumab and methotrexate showed improvement in clinical signs and symptoms of RA, compared to only 25% in patients receiving methotrexate alone.

**Useful For:**

- Evaluation of patients with suspected systemic infection
- Evaluation of patients with suspected localized infection, specifically prosthetic joint infection (PJI)
- Evaluation of patients with suspected chronic inflammatory disorders, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, or inflammatory bowel disease

**Interpretation:** Elevated concentrations of interleukin-6 (IL-6) may indicate an ongoing inflammatory response and could be consistent with a systemic infection, localized infection, or chronic inflammatory disease.

**Reference Values:**

< or =1.8 pg/mL

**Clinical References:**

Interleukin-10 (IL-10) Serum
Reference Values:
<2.0 pg/mL

Interleukin-4 (IL-4) Serum
Reference Values:
<2.0 pg/mL

Interleukin-8 (IL-8) Serum
Reference Values:
<57.8 pg/mL

Intrinsic Factor Blocking Antibody, Serum
Clinical Information: The cobalamins, also referred to as vitamin B12, are a group of closely related enzymatic cofactors involved in the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A and in the synthesis of methionine from homocysteine. Vitamin B12 deficiency can lead to megaloblastic anemia and neurological deficits. The latter may exist without anemia, or precede it. Adequate replacement therapy will generally improve or cure cobalamin deficiency. Unfortunately, many other conditions, which require different interventions, can mimic the symptoms and signs of vitamin B12 deficiency. Moreover, even when cobalamin deficiency has been established, clinical improvement may require different dosages or routes of vitamin B12 replacement, depending on the underlying cause. In particular, patients with pernicious anemia (PA), possibly the commonest type of cobalamin deficiency in developed countries, require either massive doses of oral vitamin B12 or parenteral replacement therapy. The reason is that in PA patients suffer from gastric mucosal atrophy, most likely caused by a destructive autoimmune process. This results in diminished or absent gastric acid, pepsin and intrinsic factor (IF) production. Gastric acid and pepsin are required for liberation of cobalamin from binding proteins, while IF binds the free vitamin B12, carries it to receptors on the ileal mucosa, and facilitates its absorption. Most PA patients have autoantibodies against gastric parietal cells or intrinsic factor, with the latter being very specific but only present in approximately 50% of cases. By contrast, parietal cell antibodies are found in approximately 90% of PA patients, but are also found in a significant proportion of patients with other autoimmune diseases, and in approximately 2.5% (4th decade of life) to approximately 10% (8th decade of life) of healthy individuals.

Useful For: Confirming the diagnosis of pernicious anemia

Interpretation: The aim of the work-up of patients with suspected vitamin B12 deficiency is to first confirm the presence of deficiency and then to establish its most likely etiology. Measurement of serum vitamin B12, either preceded or followed by serum methylmalonic acid measurement, is the first step in diagnosing pernicious anemia (PA). If these tests support deficiency, then intrinsic factor blocking antibody (IFBA) testing is indicated to confirm PA as the etiology. A positive IFBA test supports very strongly a diagnosis of PA. Since the diagnostic sensitivity of IFBA testing for PA is only around 50%, an indeterminate or negative IFBA test does not exclude the diagnosis of PA. In these patients, either PA or another etiology, such as malnutrition, may be present. Measurement of serum gastrin levels will help in these cases. In patients with PA, fasting serum gastrin is elevated to more than 200 pg/mL in an attempted compensatory response to the achlorhydria seen in this condition. For a detailed overview of the optimal testing strategies in PA diagnosis, see ACASM / Pernicious Anemia Cascade, Serum and associated Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:
Negative

Iodine, 24 Hour, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

Useful For: Assessment of iodine toxicity or recent exposure in a 24-hour urine collection Monitoring iodine excretion rate as index of replacement therapy

Interpretation: Measurement of urinary iodine excretion provides the best index of dietary iodine intake and deficiency is generally indicated when the concentrations are below 100 mcg/L.

Reference Values:
0-17 years: not established
> or =18 years: 75-851 mcg/24 hour


Iodine, Serum

Clinical Information: Iodine is an essential element that is required for thyroid hormone production. The measurement of iodine serves as an index of adequate dietary iodine intake and iodine overload, particularly from iodine-containing drugs such as amiodarone.

Useful For: Determination of iodine overload using serum specimens Monitoring iodine levels in individuals taking iodine-containing drugs

Interpretation: Values between 80 ng/mL and 250 ng/mL have been reported to indicate hyperthyroidism. Values above 250 ng/mL may indicate iodine overload.

Reference Values:
40-92 ng/mL

**ICRU 60440**

**Iodine/Creatinine Ratio, Random, Urine**

**Clinical Information:** Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

**Useful For:** Assessment of iodine toxicity or recent exposure when a 24-hour urine cannot be collected. Monitoring iodine excretion rate as index of replacement therapy when a 24-hour urine cannot be collected.

**Interpretation:** Measurement of urinary iodine excretion provides the best index of dietary iodine intake and deficiency is generally indicated when the concentrations are below 100 mcg/L. For deficiency, 10 repeat random urines are recommended.

**Reference Values:**
- 0-17 years: not established
- > or = 18 years: <584 mcg/g creatinine

**Clinical References:**

**HEXP 61713**

**Iohexol, Plasma**

**Clinical Information:** The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Plasma concentrations of iohexol can be used for measurement of GFR through multiple plasma iohexol determinations following an intravenous bolus injection of iohexol (plasma disappearance), or following a continuous infusion (or subcutaneous injection) of iohexol when used in conjunction with urine iohexol determinations (urinary clearance; HEXU / Iohexol, Timed Collection, Urine).

**Useful For:** Determining glomerular filtration rate in plasma specimens

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

**HEXU 61712**

**Iohexol, Timed Collection, Urine**

**Clinical Information:** The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Plasma concentrations of iohexol can be used for measurement of GFR through multiple plasma iohexol determinations following an intravenous bolus injection of iohexol (plasma disappearance), or following a continuous infusion (or subcutaneous injection) of iohexol when used in conjunction with urine iohexol determinations (urinary clearance; HEXU / Iohexol, Timed Collection, Urine).

**Useful For:** Determining glomerular filtration rate in plasma specimens

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1469
research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Urine concentrations of iohexol can be used for measurement of GFR following a subcutaneous injection of iohexol (plasma disappearance), or during a continuous infusion of iohexol when used in conjunction with plasma iohexol determinations (HEXP / Iohexol, Plasma). The results can be used to determine the clearance of iohexol, which is a measure of GFR.

**Useful For:** Determining glomerular filtration rate in urine specimens

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

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**FIPEC**

91134

**Ipecac Use Markers**

**Reference Values:**
Therapeutic and toxic ranges have not been established.
Emetine and cephaeline are alkaloids present in ipecac.
Serum emetine levels within 2 hours of a 30 mL dose of ipecac syrup range from 0 - 75.0 ng/mL.

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**FEC**

34624

**Iron and Total Iron-Binding Capacity, Serum**

**Clinical Information:** Ingested iron is absorbed primarily from the intestinal tract and is temporarily stored in the mucosal cells as ferritin (Fe[III]). Ferritin provides a soluble protein shell to encapsulate a complex of insoluble ferric hydroxide-ferric phosphate. On demand, iron is released into the blood by mechanisms that are not clearly understood, to be transported as Fe(III)-transferrin. Transferrin is the primary plasma iron transport protein, which binds iron strongly at physiological pH. Transferrin is generally only 25% to 30% saturated with iron. The additional amount of iron that can be bound is the unsaturated iron-binding capacity (UIBC). The total iron-binding capacity (TIBC) can be indirectly determined using the sum of the serum iron and UIBC. Knowing the molecular weight of the transferrin and that each molecule of transferrin can bind 2 atoms of iron, TIBC and transferrin concentration is interconvertible. Percent saturation (100 x serum iron/TIBC) is usually normal or decreased in persons who are iron deficient, pregnant, or are taking oral contraceptive medications. Persons with chronic inflammatory processes, hemochromatosis, or malignancies generally display low transferrin. Serum iron, total iron-binding capacity, and percent saturation are widely used for the diagnosis of iron deficiency. However, serum ferritin is a much more sensitive and reliable test for demonstration of iron deficiency.

**Useful For:** Screening for chronic iron overload diseases, particularly hereditary hemochromatosis

**Interpretation:** In hereditary hemochromatosis, serum iron is usually above 150 mcg/dL and percent saturation is above 60%. In advanced iron overload states, the percent saturation often is above 90%. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

**Reference Values:**
IRON
Males: 50-150 mcg/dL
Females: 35-145 mcg/dL
TOTAL BINDING CAPACITY
250-400 mcg/dL

PERCENT SATURATION
14-50%


Iron, Liver Tissue

Clinical Information: Hemosiderosis is the condition of excessive iron accumulation in tissues. Liver is the first organ affected in iron-overload diseases. Transient increases in iron first appear in Kupffer cells. This finding is commonly related to sideroblastic anemia, excessive iron consumption, or chronic alcohol ingestion. Persistent hemosiderosis, as seen in hemochromatosis, causes iron accumulation in hepatocytes, and is usually concentrated in biliary cells. Hereditary hemochromatosis is an autosomal recessive disease with estimated prevalence in the population of 2 in 1,000 in Caucasians, with lower incidence in other races. The gene responsible for hereditary hemochromatosis (HFE) is located on chromosome 6; the majority of hereditary hemochromatosis patients have variants in this HFE gene. Hereditary hemochromatosis is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues that typically begins to be expressed in the third to fifth decades of life, but may occur in children. The most common presentation is hepatic cirrhosis in combination with hypopituitarism, cardiomyopathy, diabetes, arthritis, or hyperpigmentation. Because of the severe sequelae of this disease if left untreated and recognizing that treatment is relatively simple, early diagnosis before symptoms or signs appear is important. Screening for hemochromatosis is best done by measuring serum iron and transferrin saturation (FEC / Iron and Total Iron-Binding Capacity, Serum). If the serum iron concentration is above 175 mcg/dL and the transferrin saturation is above 55%, analysis of serum ferritin concentration (FERR / Ferritin, Serum) is indicated. A ferritin concentration above 400 ng/mL is suggestive of hemochromatosis, but also can indicate other forms of hepatocyte injury such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver. HFE analysis (HFE / Hemochromatosis HFE Gene Analysis, Blood) may be used to confirm the clinical diagnosis of hemochromatosis, to diagnose hemochromatosis in asymptomatic individuals with blood tests showing increased iron stores, or for predictive testing of individuals who have a family history of hemochromatosis. The alleles evaluated by HFE gene analysis are evident in approximately 80% of patients with hemochromatosis; a negative report for HFE gene does not rule-out hemochromatosis. In a patient with negative HFE gene testing, elevated iron status for no other obvious reason, and family history of liver disease, additional evaluation of liver iron concentration is indicated. Diagnosis of hemochromatosis may also be based on biochemical analysis and histologic examination of a liver biopsy. In this assay, results are reported as the hepatic iron index (HII) and dry weight of iron. The HII is considered the "gold standard" for diagnosis of hemochromatosis. This test is appropriate when: -Serum iron is above 160 mcg/dL. -Transferrin saturation is above 55%. -Ferritin is above 400 ng/mL in males or above 200 ng/mL in females. -HFE gene test is negative for HFE variants See Hereditary Hemochromatosis Algorithm in Special Instructions

Useful For: Diagnosis of hemochromatosis using liver tissue specimens

Interpretation: A hepatic iron concentration above 10,000 mcg/g dry weight is diagnostic for hemochromatosis. Hepatic iron concentrations above 3,000 mcg/g are seen when there is iron overload without cellular injury and cirrhosis. Hepatic iron concentrations greater than the reference range are associated with hemosiderosis, thalassemia, and sideroblastic anemia. Some patients with hepatitis or cirrhosis without significant fibrosis will have hepatic iron concentrations at the top end of normal or just slightly above the normal range. Iron accumulates in the liver normally with aging. The hepatic iron index (HII) normalizes hepatic iron concentration for age. The HII is calculated from the hepatic iron concentration by converting the concentration from mcg/g to mcmol/g dry weight and dividing by years.
of age. The normal range for HII is less than 1.0. -Patients with homozygous hemochromatosis have an HII above 1.9. -Patients with heterozygous hemochromatosis often have an HII ranging from 1.0 to 1.9. -Patients with hepatitis and alcoholic cirrhosis usually have an HII below 1.0, although a small percentage of patients with alcoholic cirrhosis have an HII in the range of 1.0 to 1.9. -Patients with hemochromatosis who have been successfully treated with phlebotomy will have an HII below 1.0. Liver specimens collected from patients with cirrhosis containing a high degree of fibrosis have results near the low end of the reference range, even though they will show significant iron staining in hepatocytes. While it is true that iron accumulates in hepatocytes in advanced alcoholic cirrhosis with fibrosis, there are relatively few hepatocytes compared to other inert (fibrotic) tissue, so the quantitative iron determination, which is expressed as mcg of iron per gram of dry weight tissues, yields a low result. Histologic examination of all tissue specimens should be performed to facilitate correct interpretation. When structural heterogeneity is apparent histologically, variation in measured iron should be anticipated. We have observed, in approximately 2% of cases, a high degree of hepatic heterogeneity that makes quantitation highly variable.

**Reference Values:**

**IRON**
- Males: 200-2,400 mcg/g dry weight
- Females: 200-1,800 mcg/g dry weight

**IRON INDEX**
- Reference values have not been established for patients that are <13 years of age.
- <1.0 mcmol/g/year (> or =13 years)

**Clinical References:**

**Isavuconazole (CRESEMBA) LC-MS/MS**

**Clinical Information:** Isavuconazole is for the treatment of life threatening fungal infections, specifically invasive aspergillosis and invasive mucormycosis. There is a significant need for alternative antifungal therapies that address some of the limitations of voriconazole, such as reduced potential for nephrotoxicity for the intravenous formulation, in addition to other dose-related toxicities. Given the difficulty in diagnosis and similarity with which infections may present, having an antifungal that is effective for both indications would be particularly useful to physicians treating immunocompromised patients.

**Reference Values:**
- 0.1-10. mcg/mL

**Clinical References:**
**ISPCA**

**ISH Additional (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**ISA26**

**ISH Additional, Professional Only (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**ISTOA**

**ISH Additional, Tech Only (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**ISPCI**

**ISH Initial (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**ISH26**

**ISH Initial, Professional Only (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**ISTOI**

**ISH Initial, Tech Only (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**ISLET**

**Islet 1 Immunostain, Technical Component Only**

**Clinical Information:** Islet 1 is a homeobox-gene-related transcription factor involved in the development of the endocrine pancreas. Islet 1 is expressed in endocrine pancreas, subsets of neurons of the adrenal medulla, and dorsal root ganglion cell layers in the retina, the pineal gland, and some areas of the brain. Islet 1 is a useful marker as it is positive in the majority of pancreatic endocrine tumors.

**Useful For:** Identification of endocrine tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation.
evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**Islet Antigen 2 (IA-2) Antibody, Serum**

**Clinical Information:** Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus for 36 years. In recent years, several autoantigens against which islet antibodies are directed have been identified. These include the tyrosine phosphatase-related islet antigen 2 (IA-2), glutamic acid decarboxylase 65, the zinc transporter ZnT8, and insulin. One or more of these autoantibodies are detected in 96% of patients with type 1 diabetes, and are detectable before clinical onset, as well as in asymptomatic individuals. A serological study of 50 type 1 diabetics and 50 control subjects conducted simultaneously across 43 laboratories in 16 countries demonstrated a median sensitivity of 57% and a median specificity of 99% for IA-2 antibody in type 1 diabetes. Prospective studies in relatives of patients with type 1 diabetes have shown that development of 1 or more islet autoantibodies (including IA-2 antibody) provides an early marker of progression to type 1 diabetes. Autoantibody profiles identifying patients destined to develop type 1 diabetes are usually detectable before age 3. In 1 study of relatives seropositive for IA-2 antibody, the risk of developing type 1 diabetes within 5 years was 65.3%. Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom onset in adulthood, societal obesity, and initial insulin-independence. These patients with "latent autoimmune diabetes in adulthood" may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including IA-2).

**Useful For:** Clinical distinction of type 1 from type 2 diabetes mellitus Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes) Prediction of future need for insulin treatment in adult-onset diabetic patients

**Interpretation:** Seropositivity for IA-2 autoantibody (> 0.02 nmol/L) is supportive of: -A diagnosis of type 1 diabetes -A high risk for future development of diabetes -A current or future need for insulin therapy in patients with diabetes

**Reference Values:**

< or =0.02 nmol/L

Reference values apply to all ages.


**Isoagglutinin Titer, Anti-A, Serum**

**Clinical Information:** Isoagglutinins are antibodies produced by an individual that cause agglutination of RBCs in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type B or O individuals will usually possess anti-A.
The anti-A is formed in response to exposure to A-like antigenic structures found in ubiquitous non-red cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at 3 to 6 months of age. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia. Some individuals with roundworm infections will have elevated levels of anti-A.

**Useful For:** Evaluation of individuals with possible hypogammaglobulinemia

**Interpretation:** The result is reported as antiglobulin phase, in general representing IgG antibody. The result is the reciprocal of the highest dilution up to 1:1024 at which macroscopic agglutination (1+) is observed. Dilutions above 1:1024 are reported as >1024.

**Reference Values:**
Interpretation depends on clinical setting. No defined reference values.


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**Isoagglutinin Titer, Anti-B, Serum**

**Clinical Information:** Isoagglutinins are antibodies produced by an individual that cause agglutination of RBCs in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type A or O individuals will usually possess anti-B. The anti-B is formed in response to exposure to B-like antigenic structures found in ubiquitous non-red cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at 3 to 6 months of age. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia.

**Useful For:** Evaluation of individuals with possible hypogammaglobulinemia

**Interpretation:** The result is reported as antiglobulin phase, in general representing IgG antibody. The result is the reciprocal of the highest dilution up to 1:1024 at which macroscopic agglutination (1+) is observed. Dilutions above 1:1024 are reported as >1024.

**Reference Values:**
Interpretation depends on clinical setting. No defined reference values.


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**Isocitrate Dehydrogenase 1 and 2 (IDH1/IDH2) Mutation Analysis, Tumor**

**Clinical Information:** IDH1 and IDH2 (IDH) genes encode dehydrogenase enzymes that are involved in cellular glucose metabolism and oxidative damage control. IDH variants, primarily involving codons R132 in IDH1 and R172 in IDH2, result in reduction of the enzyme physiological activity and gain of a neomorphic ability to generate oncometabolite R(-)-2-hydroxyglutarate, which contribute to tumorigenesis by altering numerous cellular responses, including genome-wide epigenetic changes that characterize the glioma CpG island methylator phenotype (G-CIMP). IDH variants seem to be an early event in gliomagenesis and have been identified in over 70% of lower-grade (grades II/III) diffuse gliomas and secondary glioblastoma. These variants are rarely seen in other central nervous system tumors and are not seen in reactive non-neoplastic processes, and define a group of lower and high-grade diffuse gliomas associated with a more favorable prognosis. Assessment of IDH variant
status in central nervous system tumors may assist in tumor classification and provide prognostically relevant information for subgroups of patients with diffuse gliomas. IDH1 and IDH2 gene variants are also observed in a variety of non-CNS tumor types. Assessment of IDH variant status may assist in the differential diagnosis of chondroid bone tumors and provide prognostically relevant information in other contexts, such as in the setting of acute myeloid leukemia (AML).

**Useful For:** Supporting a morphological diagnosis of a diffuse glioma Assisting in central nervous system tumor classification Stratifying prognosis of diffuse gliomas Supporting the differential diagnosis of chondroid bone tumors Stratifying prognosis of acute myeloid leukemia

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Isocyanate HDI, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to isocyanate HDI Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>

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### Isocyanate MDI, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to isocyanate MDI Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Isocyanate TDI, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to isocyanate TDI, Defining the allergen responsible for eliciting signs and symptoms, Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
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**Isoniazid (INH)**

**Reference Values:**

Units: ug/mL

The effective concentration range of isoniazid is dependent upon the minimum inhibitory concentration of the pathogen being treated.

Toxic range: greater than 20 ug/mL.
ISPG
82768

Ispaghula, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ispaghula
Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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ITCON
81247

Itraconazole, Serum

Clinical Information: Itraconazole is a synthetic triazole antifungal drug approved for treatment and prophylaxis of a variety of fungal infections. Its activity results from inhibition of fungal synthesis of ergosterol, an integral component of fungal cell membranes. Concerns about adequate absorption and drug interactions are some of the major indications for therapeutic drug monitoring. Mean oral bioavailability approximates 55% but is highly variable; absorption can be enhanced by food or acidic drinks. Hepatic enzyme inducers can cause low serum itraconazole levels, and coadministration of these drugs has been associated with itraconazole therapeutic failure. Itraconazole therapeutic efficacy is greatest when serum concentrations exceed 0.5 mcg/mL for localized infections, or 1.0 mcg/mL for systemic infections. An active metabolite, hydroxyitraconazole, is present in serum at roughly twice the
level of the parent drug. These concentrations refer to analysis by high-performance liquid chromatography; quantitation by bioassay results in considerably higher apparent drug measurements due to reactivity with the active metabolite.

**Useful For:** Verifying systemic absorption of orally administered itraconazole Patients with life-threatening fungal infections Patients considered at risk for poor absorption or rapid clearance of itraconazole

**Interpretation:** A lower cutoff concentration has not been defined that applies in all cases. The serum concentration must be interpreted in association with other variables, such as the nature of the infection, the specific microorganism, and minimal inhibitory concentration (MIC) results, if available. Localized infections are more likely to respond when serum itraconazole is more than 0.5 mcg/mL (by high-performance liquid chromatography); systemic infections generally require drug concentrations more than 1.0 mcg/mL. Consider target of more than 1.5 mcg/mL for itraconazole plus hydroxyitraconazole.

**Reference Values:**

**ITRACONAZOLE (TROUGH)**

- >0.5 mcg/mL (localized infection)
- >1 mcg/mL (systemic infection)

**HYDROXYITRACONAZOLE**

No therapeutic range established; activity and serum concentration are similar to parent drug.

**Clinical References:**


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**JCHAI**

**J-Chain Immunostain, Technical Component Only**

**Clinical Information:** J chain is a small, glycopeptide of 15 kDa that is structurally unrelated to heavy or light chains. It serves to structurally link the immunoglobulin components of polymeric immunoglobulins IgA and IgM, and it appears to play a role in secretion of antibodies at mucosal sites. B cells in the germinal center express J chain at an early stage of differentiation, with the expression persisting in the plasma cells destined to produce IgA or IgM.

**Useful For:** Classification of lymphomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**JMACK**

**Jack Mackerel, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Jack mackerel
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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</tr>
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</table>

Reference values apply to all ages.


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**JAK2F 64980**

**JAK2 (9p24.1) Rearrangement for Hematologic Disorders, FISH**

**Clinical Information:** The JAK2 gene is a protein tyrosine kinase involved in cytokine signaling. Chromosomal translocations involving JAK2 can lead to the formation of chimeric oncoproteins in hematologic malignancies. Rearrangements involving 9p24.1 are typically aggressive and rare abnormalities seen in various hematologic diseases. JAK2 inhibitors are one of the only therapy options besides a stem cell transplant for JAK2 rearrangements.

**Useful For:** Providing diagnostic information and helping to determine whether a targeted JAK2 inhibitor could be useful for therapy

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the JAK2 locus. A negative result suggests no rearrangement of the JAK2 gene region at 9p24.1.
**JAK2P**

**JAK2 (9p24.1) Rearrangement, Hematologic Disorders, FISH, Tissue**

**Clinical Information:** The JAK2 gene codes for a protein tyrosine kinase involved in cytokine signaling. Chromosomal translocations involving JAK2 can lead to the formation of chimeric oncoproteins in hematologic malignancies. Rearrangements involving 9p24.1 are rare abnormalities seen in various hematologic diseases and are typically aggressive. Identification of opportunities to apply targeted therapy with JAK2 inhibitors can be helpful for patients with JAK2 rearrangements.

**Useful For:** Providing diagnostic information for hematologic malignancies Aiding in the determination of whether a targeted JAK2 inhibitor could be useful for therapy

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the JAK2 locus. A negative result suggests no rearrangement of the JAK2 gene region at 9p24.1.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**JAKXB**

**JAK2 Exon 12 and Other Non-V617F Mutation Detection, Blood**

**Clinical Information:** DNA sequence mutations in the Janus kinase 2 gene (JAK2) are found in the hematopoietic cells of several myeloproliferative neoplasms (MPN), most frequently polycythemia vera (close to 100%), essential thrombocytopenia (approximately 50%), and primary myelofibrosis (approximately 50%). Mutations in JAK2 have been reported at much lower frequency in other MPN, chronic myelomonocytic leukemia and mixed MPN/myelodysplastic syndromes, but essentially never in chronic myelogenous leukemia (CML), reactive cytoses, or normal patients. Mutations are believed to cause constitutive activation of the JAK2 protein, which is an intracellular tyrosine kinase important for signal transduction in many hematopoietic cells. Since it is often difficult to distinguish reactive conditions from the non-CML MPN, identification of a JAK2 mutation has diagnostic value. Potential prognostic significance of JAK2 mutation detection in chronic myeloid disorders has yet to be clearly established. The vast majority of JAK2 mutations occur as base pair 1849 in the gene, resulting in a JAK2 V617F protein change. In all cases being evaluated for JAK2 mutation status, the initial test that should be ordered is JAK2B / JAK2 V617F Mutation Detection, Blood, a sensitive assay for detection of the mutation. However, if no JAK2 V617F mutation is found, further evaluation of JAK2 may be clinically indicated. Over 50 different mutations have now been reported within exons 12 through 15 of JAK2 and...
essentially all of the non-V617F mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, research in this area is ongoing. This assay for non-V617F/alternative JAK2 mutations is designed to obtain the sequence for JAK2 exons 12 through the first 90% of exon 15, which spans the region containing all mutations reported to date.

**Useful For:** Second-order testing to aid in the distinction between a reactive cytosis and a myeloproliferative neoplasm, particularly when a diagnosis of polycythemia is being entertained; for use with blood specimens

**Interpretation:** The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**JAKXM 60025**

**JAK2 Exon 12 and Other Non-V617F Mutation Detection, Bone Marrow**

**Clinical Information:** DNA sequence mutations in the Janus kinase 2 (JAK2) gene are found in the hematopoietic cells of several myeloproliferative neoplasms (MPN), most frequently polycythemia vera (close to 100%), essential thrombocytopenia (approximately 50%), and primary myelofibrosis (approximately 50%). Mutations in JAK2 have been reported at much lower frequency in other MPN, chronic myelomonocytic leukemia and mixed MPN/myelodysplastic syndromes, but essentially never in chronic myelogenous leukemia (CML), reactive cytoses, or normal patients. Mutations are believed to cause constitutive activation of the JAK2 protein, which is an intracellular tyrosine kinase important for signal transduction in many hematopoietic cells. Since it is often difficult to distinguish reactive conditions from the non-CML MPN, identification of a JAK2 mutation has diagnostic value. Potential prognostic significance of JAK2 mutation detection in chronic myeloid disorders has yet to be clearly established. The vast majority of JAK2 mutations occur as base pair 1849 in the gene, resulting in a JAK2 V617F protein change. In all cases being evaluated for JAK2 mutation status, the initial test that should be ordered is JAK2M / JAK2 V617F Mutation Detection, Bone Marrow, a sensitive assay for detection of the mutation. However, if no JAK2 V617F mutation is found, further evaluation of JAK2 may be clinically indicated. Over 50 different mutations have now been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, research in this area is ongoing. This assay for non-V617F/alternative JAK2 mutations is designed to obtain the sequence for JAK2 exons 12 through the first 90% of exon 15, which spans the region containing all mutations reported to date.

**Useful For:** Second-order testing to aid in the distinction between a reactive cytosis and a myeloproliferative neoplasm, particularly when a diagnosis of polycythemia is being entertained; for use with bone marrow specimens
Interpretation: The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

Reference Values:
An interpretive report will be provided.


JAKXR 44178

JAK2 Exon 12-15 Sequencing, Polycythemia Vera Reflex, Varies

Clinical Information: The Janus kinase 2 (JAK2) gene codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. The JAK2 V617F is located in exon 14 and present in 50% to 60% of primary myelofibrosis and essential thrombocytopenia, and 95% to 98% of polycythemia vera (PV). In the rest of the polycythemia vera cases, over 50 different mutations have been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F JAK2 mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, some mutations may not be well characterized and requires further clinical and research evaluation.

Useful For: Aiding in the distinction between the myeloproliferative neoplasm polycythemia vera (PV) and other secondary erythrocytosis Evaluating for mutations within exons 12 to 15 of JAK2 in an algorithmic process as part of PVJAK / Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis, Varies

Interpretation: The results will be reported as 1 of the 3 following states: -Positive for JAK2 V617F mutation -Positive for JAK2 mutation (other than V617F) -Negative for JAK2 mutations If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence are reported. A positive mutation status is highly suggestive of a myeloid neoplasm and may support a diagnosis of polycythemia vera in the appropriate clinical setting. Correlation with clinicopathologic findings and other laboratory results is necessary in all cases. A negative mutation status makes a diagnosis of polycythemia vera highly unlikely, although it does not completely exclude this possibility, other myeloproliferative neoplasms or other neoplasms.

Reference Values:
Only orderable as a reflex. For more information, see PVJAK / Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis, Varies.

An interpretive report will be provided.


**JAK2 V617F Mutation Detection, Blood**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This variant is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F variant is present in 95% to 98% of polycythemia vera patients, 50% to 60% of primary myelofibrosis patients, and 50% to 60% of essential thrombocytopenia patients. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This variant is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F variant is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET).(5-9) Variants in JAK2, CALR, and MPL are essentially mutually exclusive.

**Useful For:** Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder in peripheral blood specimens

**Interpretation:** The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F variant -Positive for JAK2 V617F variant Positive variant status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

**Reference Values:**
An interpretive report will be provided.


**JAK2 V617F Mutation Detection, Bone Marrow**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative
neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This variant is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F variant is present in 95% to 98% of polycythemia vera patients, 50% to 60% of primary myelofibrosis (PMF) patients, and 50% to 60% of essential thrombocytemia (ET) patients. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This variant is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F variant is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive.

**Useful For:** Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder in bone marrow specimens

**Interpretation:** The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F variant -Positive for JAK2 V617F variant Positive variant status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation
-Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.


Jalapeno/Chipotle (Capsicum annuum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

Japanese Cedar, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Japanese cedar

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FJCV 91827 JC Polyoma Virus DNA, Quantitative Real-Time PCR, Plasma

Clinical Information: JC Virus is the cause of Progressive multifocal Leukoencephalopathy (PML), a severe demyelinating disease of the central nervous system. PML is a particular concern for individuals infected with the human immunodeficiency virus. Quantification of JC virus DNA is based upon the real-time PCR amplification and detection of JCV genomic DNA. The quantitative range of this assay is 500-35,000,000 JCV DNA copies/mL.

Reference Values:
<500 copies/mL

JCV 70475 JC Virus Detection by In Situ Hybridization

Clinical Information: JC virus (JCV) is the etiologic agent of progressive multifocal leukoencephalopathy (PML), a rare, demyelinating, fatal disorder of the central nervous system that occurs on a background of immune deficiency. PML is an infrequent complication of a wide variety of conditions, including lymphoproliferative disorders (Hodgkin disease, chronic lymphocytic leukemia), sarcoidosis, tuberculosis, and AIDS.

Useful For: Confirming a clinical and histopathologic diagnosis of progressive multifocal leukoencephalopathy

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**JC Virus, Molecular Detection, PCR, Spinal Fluid**

**Clinical Information:** JC virus (JCV), a member of the genus Polyomavirus, is a small nonenveloped DNA-containing virus. Primary infection occurs in early childhood, with a prevalence of greater than 80%. The virus is latent but can reactivate in immunosuppressed patients, especially those with AIDS. JCV is recognized as the etiologic agent of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system. Histologic examination of brain biopsy tissue may reveal characteristic pathologic changes localized mainly in oligodendrocytes and astrocytes. Detection of JCV DNA by PCR (target gene, large T antigen) in the cerebrospinal fluid specimens of patients with suspected PML infection has replaced the need for biopsy tissue for laboratory diagnosis. Importantly, the PCR test is specific with no cross-reaction with BK virus, a closely related polyomavirus.

**Useful For:** Aids in diagnosing progressive multifocal leukoencephalopathy due to JC virus (JCV)

This test is not to be used as a diagnostic tool for Creutzfeldt-Jakob disease (CJD).

**Interpretation:** Detection of JC virus (JCV) DNA supports the clinical diagnosis of progressive multifocal leukoencephalopathy due to JCV.

**Reference Values:**
Negative

**Clinical References:**

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**Jo 1 Antibodies, IgG, Serum**

**Clinical Information:** Jo 1 (histidyl tRNA synthetase) is a member of the amino acyl-tRNA synthetase family of enzymes found in all nucleated cells. Jo 1 antibodies in patients with polymyositis bind to conformational epitopes of the enzyme protein and inhibit its catalytic activity in vitro. Jo 1 antibodies are a marker for the disease polymyositis, and occur most commonly in myositis patients who also have interstitial lung disease. The antibodies occur in up to 50% of patients with interstitial pulmonary fibrosis and symmetrical polyarthritis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms compatible with a connective tissue disease, especially those patients with muscle pain and limb weakness, concomitant pulmonary signs and symptoms, Raynaud phenomenon, and arthritis. Testing for antibodies to Jo 1 is not useful in patients with a negative test for antinuclear antibodies.

**Interpretation:** A positive result for Jo 1 antibodies is consistent with the diagnosis of polymyositis and suggests an increased risk of pulmonary involvement with fibrosis in such patients.

**Reference Values:**

<1.0 U (negative)
> or =1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**
Johnson Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Johnson grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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Reference values apply to all ages.


June Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in
infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to June grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
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<tr>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FWJR 57953**

**Juniper Western (Juniperus occidentalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

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**KLISH 70615**

**Kappa and Lambda Light Chain mRNA, In Situ Hybridization (ISH) Technical Component Only**

**Clinical Information:** Restricted expression of immunoglobulin light chains can help support a diagnosis of a plasmacytic neoplasm.

**Useful For:** Aids in diagnosing plasma cell neoplasms

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a
qualified pathologist.


**KAIHC 70482**

**Kappa Light Chain Immunostain, Technical Component Only**

**Clinical Information:** Kappa or lambda immunoglobulin light chains pair with immunoglobulin heavy chains to form complete immunoglobulin molecules. These proteins serve as receptors for antigens in B lymphocytes and are the secretory products of plasma cells, forming the humoral arm of the immune system. Because individual B cells or plasma cells synthesize immunoglobulin containing either kappa or lambda light chains, but not both, immunoperoxidase stains for light chains can be applied to lymphocyte and plasma cell populations as a marker of clonality and B-cell lineage.

**Useful For:** A marker of clonality and B-cell lineage

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**KAIPC 113330**

**KappaLambda IHC (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**KCNN4 607809**

**KCNN4 Full Gene Sequencing, Varies**

**Clinical Information:** Dehydrated hereditary stomatocytosis (DHSt) 2 (also called hereditary xerocytosis) is an autosomal dominant hereditary hemolytic disorder caused by an abnormal cation leak in the red cell membrane, resulting in loss of a potassium cation and red blood cell dehydration. Pseudohyperkalemia (loss of red cell potassium when cold or at room temperature) can be a feature. Symptoms include compensated to mild hemolytic anemia, moderate splenomegaly, elevated reticulocyte count, increased mean corpuscular volume (MCV), variably increased mean corpuscular hemoglobin concentration (MCHC), perinatal edema, and a tendency for iron overload. Red cells exhibit various shape abnormalities on blood smear, including elliptocytes, schizocytes, and rare stomatocytes. The majority of symptomatic DHSt cases reported to date have been associated with gain-of-function alterations in the mechanosensitive cation channel gene, PIEZO1. However, recent studies have identified families with DHSt associated with variants in the KCNN4 gene.(1-4) KCNN4 encodes for the Gardos channel, the erythroid voltage-independent potassium channel that is activated by intracellular calcium.(4) Pathogenic alterations in KCNN4 result in decreased intracellular total cation and potassium levels. Cases reported
have shown abnormal ektacytometry curves typical of hereditary xerocytosis. Clinical features of KCNN4 patients include hemolytic anemia of variable severity that can be more severe in the perinatal period. Splenectomy may have no efficacy in symptom improvement in the few cases with KCNN4 variants.2, 5 This test is best interpreted in the context of protein studies and peripheral blood findings. This can be provided by also ordering RBCME / Red Blood Cell Membrane Evaluation, Blood. Please fill out the information sheet and indicate that KCNN4 testing was ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results.

**Useful For:** Genetic confirmation of a dehydrated hereditary stomatocytosis (DHSt) or hereditary xerocytosis diagnosis with the identification of an alteration known or suspected to cause disease in the KCNN4 gene Second-tier testing for patients in whom previous targeted gene variant analyses were negative for a specific RBC membrane disorder Establishing a diagnosis of a hereditary RBC membrane disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.


**Keratin (34BE12) Immunostain, Technical Component Only**

**Clinical Information:** Keratin 34 beta E12 (sometimes referred to as Keratin 903) is a monoclonal antibody that reacts with high-molecular-weight cytokeratin. In normal prostate, reactivity for keratin 34BE12 can be seen in the basal layer of prostatic glands in a membranous/cytoplasmic pattern. It is most useful as a basal cell-specific marker in the prostate, and shows loss of staining around glands of prostate cancer, which do not have a basal cell layer.

**Useful For:** Identification of cells expressing high-molecular-weight cytokeratin

**Interpretation:** This test does not include pathologist interpretation: only technical performance of
the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KRTAE 70493 Keratin (AE1/AE3) Immunostain, Technical Component Only

Clinical Information: Keratin clone AE1/AE3 is a broad-spectrum cytokeratin antibody that reacts with many low- and high-molecular weight-keratins in a filamentous or membrane pattern in the epithelium of most organs. Diagnostically, antikeratin antibodies are usually applied as part of a panel to determine cell lineage of poorly differentiated malignant tumors.

Useful For: Aiding in the identification of cells expressing a broad spectrum of cytokeratins (low- and high-molecular-weight keratins)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KRTCA 70494 Keratin (CAM 5.2) Immunostain, Technical Component Only

Clinical Information: The keratin antibody clone CAM 5.2 reacts with the low-molecular-weight (LMW) cytokeratins CK8 and CK7. All simple (one-layered, polar) epithelial cells contain the paired CK8 and CK18, representing the primary (constitutive) CKs of simple epithelia. These LMW CKs are the only CKs found in some simple epithelium (hepatocytes, pancreatic acini, most endocrine cells and proximal renal tubules). CAM 5.2 reacts with cells in a filamentous pattern within the cytoplasm.

Useful For: Aiding in the identification of cells expressing low-molecular-weight cytokeratins (CK7 and CK8)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Keratin (OSCAR) Immunostain, Technical Component Only

**Clinical Information:** The OSCAR cytokeratin antibody covers a wide spectrum of molecular weights; similar in expression pattern to CAM5.2, with greater coverage of high-molecular-weight range (eg, squamous epithelium). In normal tonsil, the squamous epithelium shows strong staining, and fibroblastic reticulum cells in interfollicular regions show weaker staining. Diagnostically, antikeratin antibodies are usually applied as part of a panel to determine cell lineage of poorly differentiated malignant tumors.

**Useful For:** Aids in determining primary site in carcinomas of unknown origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:** Gown AM, Yaziji H, Barry TS, et al: OACAR, a novel broad anti-cytokeratin monoclonal antibody optimized for diagnostic immunohistochemistry. Poster, United States and Canadian Academy of Pathology Annual Meeting 2003
KRT20

Keratin 20 (KRT20) Immunostain, Technical Component Only

Clinical Information: Cytokeratin 20 stains the cytoplasm of epithelial cells in a granular and/or filamentous pattern, or may appear membrane associated (cytoskeletal) with expression primarily restricted to the epithelium of the lower gastrointestinal tract, urothelium, and Merkel-cells. When used together, Cytokeratin 7 and Cytokeratin 20 may be useful as an aid in determining primary site in carcinomas of unknown origin. Cytokeratin 20 is usually positive in colon carcinomas.

Useful For: Aids in determining the primary site in carcinomas of unknown origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KRT5

Keratin 5 (KRT5) Immunostain, Technical Component Only

Clinical Information: Keratin 5 is a type II cytokeratin that dimerizes with the type I cytokeratin 14 forming intermediate filaments in the basal layer of the epidermis. Squamous epithelium of normal skin stains in a cytoplasmic pattern with keratin 5. Keratin 5 is usually positive in mesotheliomas and negative in adenocarcinomas, making it useful in separating mesotheliomas from pulmonary adenocarcinomas.

Useful For: Differentiation of mesothelioma and squamous cell carcinoma versus adenocarcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a
control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KRT7
70488

**Keratin 7 (KRT7) Immunostain, Technical Component Only**

**Clinical Information:** Keratin 7 (KRT7) stains the cytoplasm of epithelial cells in a granular and/or filamentous pattern, or may appear membrane associated (cytoskeletal). In normal tissues, KRT7 is found in a large number of cell types including many ductal and glandular epithelia (biliary and pancreatic ducts, lung alveoli, breast, ovary, endometrium, renal collecting ducts, urothelium, thyroid, placental trophoblasts, and mesothelium). When used together, KRT7 and KRT20 may be useful as an aid in determining the primary site in carcinomas of unknown origin.

**Useful For:** Aiding in determining the primary site in carcinomas of unknown origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FKEMS
75730

**Ketamine and Metabolite Screen, Plasma**

**Reference Values:**

Reporting limit determined each analysis

Units: ng/mL

Norketamine: None Detected

The intravenous administration of 2 mg/kg of Ketamine followed by continuous infusion of 41 mcg/kg/minute produced steady-state plasma concentration of 2200 ng Ketamine/mL and an average peak Norketamine level of 1050 ng/mL which occurred near the end of the 3 hour infusion.

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
Ketamine: None Detected
Reported levels during anesthesia: 500-6500 ng/mL

FKETO

Ketoconazole, Serum/Plasma
Reference Values:
Reporting limit determined each analysis

Peak plasma levels of 5.4 +/- 1.7 mcg/mL occurred at approximately 1 hour following a single 200 mg dose and peak plasma levels of 22 +/- 3 mcg/mL occurred at approximately 2 hours following a single 800 mg dose of ketoconazole.

KETGP

Ketone Disorders Gene Panel, Varies

Clinical Information: Ketones are a chemical energy source used by tissues when glucose is low. Disorders of impaired ketone body metabolism include beta-ketothiolase (BKT) deficiency and succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency. Disorders of ketogenesis are mitochondrial 3-hydroxy-3-methylglutaric acid CoA (HMG-CoA) synthase (mHS) and HMG-CoA lyase (HL) deficiencies. BKT deficiency is caused by impaired activity of the enzyme acetoacetyl-CoA thiolase. Individuals with BKT deficiency are typically asymptomatic at birth, and symptoms are likely to develop from 6 to 18 months of age with illness or fasting, which appear as episodes of decompensation and severe ketoacidosis, vomiting, dehydration, and lethargy. Children are usually asymptomatic between episodes. SCOT deficiency is a more severe ketone utilization disorder, as all experience recurrent ketoacidotic episodes, and most individuals have chronic ketosis. About 50% of infants with SCOT deficiency present in the first week of life, and the remaining 50% present between 6 to 24 months of age. mHS deficiency is due to reduced activity of a mitochondrial enzyme mHS. Infants with mHS deficiency have episodes of hypoketotic hypoglycemia, which can progress to coma. In mHS deficiency, there is no diagnostic pattern of organic acids in urine. The only biochemical diagnostic test is enzyme assay of mHS in liver. HL deficiency is due to reduced activity of mitochondrial and peroxisomal enzyme HL. Infants and children with HL deficiency also experience hypoketotic hypoglycemic episodes, and long term impacts of these episodes can include epilepsy, intellectual disability, and white matter changes in the brain, usually due to hypoglycemia. Urine organic acids of individuals with HL are characteristic and demonstrate high levels of HMG and leucine metabolites. All 4 of these ketone disorders are inherited in an autosomal recessive manner. BKT deficiency is caused by variants in ACAT1, and SCOT deficiency is caused by variants in the OCT1. HMG-CoA synthase deficiency is due to variants in HMGCS2, and HMG-CoA lyase deficiency is due to variants in HMGCL. An additional disorder that impacts ketone metabolism and is included in this panel is monocarboxylate transporter 1 deficiency, due to 2 variants in SLC16A1 and resulting in severe episodes of ketoacidosis with illness or fasting. Treatment for these ketone disorders involves avoidance of fasting and provision of oral or intravenous carbohydrate to correct hypoglycemia and ketoacidosis. Long term neurologic sequelae occur in some individuals and are a consequence of hypoglycemia during ketoacidotic episodes. Urine organic acids (OAU/Organic Acids Screen, Urine) and plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma) are the recommended first-tier tests for assessment of ketone disorders. However, as these may be normal in all but severe BKT deficiency, molecular genetic testing is a rapid and effective tool to diagnose individuals with ketone disorder.

Useful For: Follow up for abnormal biochemical results suggestive of a ketone disorder Establishing a molecular diagnosis for patients with ketone disorders Identifying variants within genes known to be associated with ketone disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Ketones, Urine**

**Clinical Information:** The body normally metabolizes fats to carbon dioxide and water. Inadequate carbohydrate in the diet or defects in carbohydrate metabolism or absorption cause the body to metabolize fatty acids. Ketones (acetoacetic acid, acetone, and beta-hydroxybutyric acid) are produced during fat metabolism and are excreted in urine. Patients with untreated or inadequately treated diabetes mellitus are unable to efficiently utilize glucose due to insufficient insulin. Under these conditions, large amounts of fatty acids are metabolized, and abnormal amounts of ketones are excreted in the urine (ketonuria). Increased ketones may occur during physiological stress conditions such as fasting, starvation, pregnancy, strenuous exercise, fever, frequent vomiting, anorexia, and some inborn errors of metabolism.

**Useful For:** Screening for the presence of ketoacidosis

**Interpretation:** Detection of ketones in the urine of a diabetic is significant and indicates a change in insulin dosage or other alteration in treatment is necessary. Ketones may appear in urine in large amounts before serum ketone is elevated.

**Reference Values:** Negative

**Clinical References:**

**Ki-67 (MIB-1) Immunostain, Technical Component Only**

**Clinical Information:** Ki-67 (antibody clone MIB-1), is a nuclear protein playing a pivotal role in maintaining cell proliferation. Ki-67 is present in all non-G0 phases of the cell cycle. Beginning in the mid-G1, the level increases through S and G2 to reach a peak in M phase. In the end of M phase, it is rapidly catabolized. Ki-67 has been employed as a marker of proliferation and, hence, prognosis in neoplasms of many types, such as malignant lymphomas, prostatic and breast adenocarcinomas, astrocytic neoplasms, and soft tissue neoplasms.

**Useful For:** A marker of proliferation in neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality...
control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**KI67B**

**Ki-67(MIB-1), Breast, Quantitative Immunohistochemistry, Automated**

**Clinical Information:** Ki-67 (MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67 (MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with breast carcinoma

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67 (MIB-1). Quantitative Ki-67 (MIB-1) results should be interpreted within the clinical context for which the test was ordered. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

**Reference Values:**

Varies by tumor type; values reported from 0% to 100%


**KIBM**

**Ki-67(MIB-1), Breast, Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Ki-67 (MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67 (MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with breast carcinoma

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67 (MIB-1) results should be interpreted within the clinical context for which the test was ordered.
Reference Values:
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Varies by tumor type; values reported from 0% to 100%

Clinical References:

Ki-67(MIB-1), Gastrointestinal/Pancreatic Neuroendocrine Tumors, Quantitative Immunohistochemistry, Automated

Clinical Information:
Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For:
Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with neuroendocrine tumors of the pancreas or gastrointestinal tract including metastases

Interpretation:
Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

Reference Values:
Varies by tumor type; values reported from 0% to 100%

Clinical References:
5. Pathology and Genetics Tumours of Endocrine Organs. Edited by RA DeLellis, RV Lloyd, PU Heitz, C Eng. IARC Press, 2004

Ki-67(MIB-1), Gastrointestinal/Pancreatic Neuroendocrine Tumors, Quantitative Immunohistochemistry, Manual

Clinical Information:
Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For:
Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with neuroendocrine tumors of the pancreas or gastrointestinal tract including metastases

Interpretation:
Results will be reported as a percentage of tumor cells staining positive for
Ki-67(MIB-1). Semi-quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

**Reference Values:**
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Varies by tumor type; values reported from 0% to 100%

**Clinical References:**

**Ki-67(MIB-1), Pulmonary, Quantitative Immunohistochemistry, Automated**

**Clinical Information:** Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with carcinoid or atypical carcinoid of the lung including metastases

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

**Reference Values:**
Varies by tumor type; values reported from 0% to 100%


**Ki-67(MIB-1), Pulmonary, Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with carcinoid or atypical carcinoid of the lung including metastases, using a manual method

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Semi-quantitative Ki-67(MIB-1) results should be interpreted within the clinical context.
Ki67 + Melan A Immunostain, Technical Component Only

Clinical Information:
Ki-67 (clone MIB-1) is a nuclear protein (detected by the chromogen DAB) playing a pivotal role in maintaining cell proliferation. Ki-67 is present in late G1-, S-, M-, and G2-phases of the cell cycle. Cells in the G0 (quiescent) phase are negative for this protein. Melan-A or melanoma antigen recognized by T cells (MART-1) (detected by the chromogen Fast Red) is expressed in the cytoplasm of melanocytes. It is a sensitive and specific marker for the diagnosis of melanoma. Melan A is also found in other tumors of melanocytic origin such as clear cell sarcoma, melanotic neurofibroma, melanotic schwannoma, as well as in perivascular epithelioid cell tumor. Melan A (clone A103) cross-reacts with steroid hormone-producing cells and tumors. Consequently, adrenocortical adenomas/carcinomas and sex cord-stromal tumors of the ovary and testis may exhibit staining.

Useful For:
Ki67 is a marker of proliferation in neoplasms. Melan A aids in the identification of melanoma.

Interpretation:
This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:
bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to red kidney bean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Kidney Stone Analysis**

**Clinical Information:** The composition of urinary stones may vary from a simple crystal to a complex mixture containing several different species of crystals. The composition of the nidus (center) may be entirely different from that of the peripheral layers. Eighty percent of patients with kidney stones have a history of recurrent stone formation. Knowledge of stone composition can be useful to guide therapy of patients with recurrent stone formation. Treatment of urinary calculi is complex.(1) In an overly simplified format, the following patterns are often treated as follows: -Hyperuricuric acid stones: alkalinize urine to increase uric acid solubility. -Hypercalciuria and predominately calcium oxalate stones: acidify urine to increase calcium solubility. However, treatment also depends on urine pH and urine phosphate, sulfate, oxalate, and citrate concentrations. -Hyperoxaluria and calcium oxalate stones: increase daily fluid intake and consider reduction of daily calcium. However, daily requirements for calcium to maintain good bone formation complicate the treatment. -Magnesium ammonium phosphate stones (struvite): Investigate and treat urinary tract infection.

**Useful For:** Managing patients with recurrent renal calculi

**Interpretation:** The interpretation of stone analysis results is complex, and beyond the scope of this text. We refer you to chapter 25 of Smith LH: Diseases of the Kidney. Vol 1. Fourth edition. Edited by RW Schrier, CW Gottscholch. Boston, MA, Little, Brown and Company, 1987. Calcium oxalate stones: -Production of calcium oxalate stones consisting of oxalate dihydrate indicate that the stone is newly
formed and current urine constituents can be used to assess the importance of supersaturation. -Production of calcium oxalate stones consisting of oxalate monohydrate indicate an old (>2 months since formed) stone and current urine composition may not be meaningful. Magnesium ammonium phosphate stones (struvite): -Production of magnesium ammonium phosphate stones (struvite) indicates that the cause of stone formation was infection. -Treatment of the infection is the only way to inhibit further stone formation. Ephedrine/guaifenesin stones: -Certain herbal and over-the-counter preparations (eg, Mah Jung) contain high levels of ephedrine and guaifenesin. Excessive consumption of these products can lead to the formation of ephedrine/guaifenesin stones.

Reference Values:
The presence of a kidney stone is abnormal. A quantitative report will be provided after analysis.

Clinical References:

Kingella kingae, Molecular Detection, PCR, Blood

Clinical Information: Kingella kingae is a fastidious short Gram-negative bacillus that may colonize the oropharynx of young children. Colonization may occasionally lead to invasive disease via hematogenous dissemination, primarily in children younger than 4 years of age. This most commonly results in bone and joint infection; K kingae is the most frequent cause of osteomyelitis and septic arthritis in children aged 6 to 36 months. K kingae may also cause endocarditis, involving both native and prosthetic valves, in patients of any age and is considered part of the HACEK (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) group of organisms, known for causing culture-negative endocarditis. K kingae produces a repeat-in-toxin (RTX) toxin. Diagnosis of K kingae infection may be challenging due to the fastidious nature of the organism in culture. Evaluation of blood by PCR is a useful tool for the diagnosis of some cases of K kingae infection.

Useful For: Aiding in the diagnosis of Kingella kingae infection using whole blood specimens

Interpretation: A positive result indicates the presence of Kingella kingae DNA. A negative result indicates the absence of detectable K kingae DNA, but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of K kingae DNA in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

Clinical References:
Clinical Information: Kingella kingae is a fastidious short Gram-negative bacillus that may colonize the oropharynx of young children. Colonization may occasionally lead to invasive disease via hematogenous dissemination, primarily in children younger than 4 years of age. This most commonly results in bone and joint infection; K kingae is the most frequent cause of osteomyelitis and septic arthritis in children aged 6 to 36 months. K kingae may also cause endocarditis, involving both native and prosthetic valves, in patients of any age and is considered part of the HACEK (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) group of organisms, known for causing culture-negative endocarditis. K kingae produces a repeat-in-toxin (RTX) toxin. Diagnosis of K kingae infection may be challenging due to the fastidious nature of the organism in culture. Evaluation of cardiac, bone, joint tissue, or fluid by PCR is a useful tool for the diagnosis of some cases of K kingae infection.

Useful For: Aiding in the diagnosis of Kingella kingae infection in tissue or synovial fluid specimens

Interpretation: A positive result indicates the presence of Kingella kingae DNA. A negative result indicates the absence of detectable K kingae DNA, but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of K kingae DNA in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

Clinical References:

KITVS
607981

KIT Asp816Val Mutation Analysis, Varies

Clinical Information: Systemic mastocytosis is a hematopoietic neoplasm that can be included in the general category of chronic myeloproliferative disorders (CMPD). These neoplasms are characterized by excessive proliferation of 1 or more myeloid lineages, with cells filling the bone marrow and populating other hematopoietic sites. In systemic mastocytosis, mast cell proliferation is the defining feature, although other myeloid lineages and B cells are frequently part of the neoplastic clone. Function-altering point alterations in KIT, a gene coding for a membrane receptor tyrosine kinase, have been found in myeloid lineage cells in the majority of systemic mastocytosis cases. The most common KIT alteration is an adenine to thymine base substitution (A>T) at nucleotide position 2447, which results in an aspartic acid to valine change in the protein (Asp816Val). Much less frequently, other alterations at this same location are found and occasional cases with alterations at other locations have also been reported. Variations at the 816 codon are believed to alter the protein such that it is in a constitutively activated state. The main downstream effect of KIT activation is cell proliferation. Detection of a variant at the 816 codon is included as one of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib, a drug commonly used to treat CMPD. It is now clear that individual mast cell neoplasms are variable with respect to the number of cell lineages containing the variant; some having positivity only in mast cells and others having positivity in additional myeloid and even lymphoid lineages. The alteration has not been reported in normal tissues.

Useful For: Diagnosing systemic mastocytosis using blood or bone marrow specimens

Interpretation: The test will be interpreted as positive or negative for KIT Asp816Val.

Reference Values:
An interpretive report will be provided indicating the mutation status as positive or negative.

KIT Immunostain, Technical Component Only

Clinical Information: KIT (CD117) membrane protein is a type III tyrosine kinase growth factor receptor for stem cell factor (SCF), also known as mast cell growth factor. It is expressed in mast cells, melanocytes, and interstitial cells of Cajal. KIT is expressed in various epithelia (breast, sweat glands and salivary glands, renal tubular cells, thyroid follicular cells), testicular and ovarian interstitial cells, neurons of the central nervous system, immature myeloid cells, and trophoblastic cells. KIT staining is useful in the diagnosis of gastrointestinal stromal tumors (GISTs), germ cell tumors, mast cell disorders and acute myeloid leukemias.

Useful For: Aids in the identification of gastrointestinal stromal tumors

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KIT Mutation Exons 8-11 and 17, Hematologic Neoplasms, Sequencing, Varies

Clinical Information: Acquired mutations in the KIT gene are identified in a subset of acute myeloid leukemias (AML) characterized by inv16 or t(16;16) CBFB-MYH11 or t(8;21) RUNX1-RUNX1T1 genetic abnormalities (approximately 10%-20% of cases) and in this setting, the additional presence of KIT gene mutation has been described as an adverse prognostic factor in some studies. KIT mutations in AML tend to involve exons 8 through 11 and 17, although the p.Asp816Val (D816V) variant that is highly prevalent in systemic mastocytosis is less common in AML. Mastocytosis is a hematologic disorder characterized by abnormal mast cell expansion in the bone marrow and extramedullary organ sites (eg, skin, gastrointestinal tract). Disease can be localized to skin (ie, cutaneous mastocytosis) or present systemically, with variable features of disease aggressiveness and symptomatology. Mutations in the KIT gene are identified in a large majority of patients with both cutaneous mastocytosis (CM) and systemic mastocytosis (SM). The D816V abnormality is identified in most patients with SM and this finding represents an important minor diagnostic criterion in the 2008...
WHO classification. The D816V is less commonly seen in CM, although single nucleotide variants are present in other KIT exons. Rare cases of familial mastocytosis are also described with KIT mutations involving exons 8 and 9. Although KIT gene mutation represents an important diagnostic marker for SM, the number of bone marrow mast cells is often limited in aspirate samples. Therefore, if SM is clinically and pathologically suspected, KIT testing should first proceed with a sensitive and specific screen for the D816V (KITB / KIT Asp816Val Mutation Analysis, Blood; KITBM / KIT Asp816Val Mutation Analysis, Qualitative PCR, Bone Marrow; or KITAS / KIT Asp816Val Mutation Analysis, Qualitative PCR) prior to consideration of KIT gene sequencing, based on the greatly enhanced sensitivity of the PCR test for this particular variant. In AML, KIT sequencing is preferred, given the wider spectrum of mutations in other KIT exons.

**Useful For:** Prognostic assessment of acute myeloid leukemias with core-binding factor translocations (inv16 or t[16;16] CBFB-MYH11 or t[8;21] RUNX1-RUNX1T1) Aids in establishing the diagnosis in some cases of mastocytosis

**Interpretation:** Mutations detected or not detected. An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided

**Clinical References:**

**Kiwi Fruit, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to kiwi fruit Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class IgE kU/L Interpretation
**Known 45,X, Mosaicism Reflex Analysis, FISH, Whole Blood**

**Clinical Information:** This test is appropriate for use in individuals with a karyotype of 45, X. Ullrich-Turner syndrome (UTS), also called Turner syndrome, is a genetic disorder associated with the apparent loss of a sex chromosome. Routine cytogenetic methods have identified 3 types of chromosomal abnormalities in UTS patients: loss of an entire X chromosome (45,X), structural X chromosome abnormalities, and mosaicism with an X or Y abnormality. In mosaicism, 2 or more populations of cells with different karyotypes are present (eg, 45,X/47,XXX). The incidence of UTS is approximately 1 in 3,000 newborn girls. Many of these patients demonstrate the 45,X karyotype. About 30% to 50% are mosaic, with either a 45,X/46,XX karyotype or a structurally abnormal X chromosome. Fewer than 15% of patients with UTS appear to have mosaicism with a 46,XY cell population or a Y chromosome rearrangement. Identifying the mosaic status of patients with UTS is of clinical importance because phenotypic expression and clinical management are dependent upon the karyotype result. Patients with a Y chromosome have a 15% to 25% increased risk of gonadoblastoma. Failure to identify an XY signal pattern does not rule out the possibility of <0.6% Y chromosome mosaicism.

**Useful For:** Detecting sex chromosome mosaicism in patients with a 45,X karyotype

**Interpretation:** An XX clone is confirmed when > or =1.0% cells display with 2 X chromosome signals. An XY clone is confirmed when > or =0.6% cells display a 1 X and 1 Y signal pattern. Females with a 45,X/46,XX karyotype have no increased risk of gonadoblastoma and generally have a more moderate expression of Turner syndrome features than females with a nonmosaic 45,X karyotype. The presence of a Y chromosome confers increased risk of gonadoblastoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**KPC (blaKPC) and NDM (blaNDM) in Gram-Negative Bacilli, Molecular Detection, PCR, Varies**

**Clinical Information:** Nonsusceptibility to carbapenems in gram-negative bacilli by means of the enzyme KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Dehli metallo-beta-lactamase) is becoming more common. The genes blaKPC and blaNDM encode KPC and NDM enzyme production,
respectively. In addition to KPC and NDM production, there are other mechanisms of resistance to carbapenems in gram-negative bacilli, including production of other carbapenemases, or plasmid-encoded AmpC, or extended beta-lactamase production combined with decreased membrane permeability. Detection of carbapenemases by the modified Hodge test may be subjective and is not rapid. Testing for the minimum inhibitory concentration (MIC) determines the level but not the mechanism of resistance. PCR is a sensitive, specific, and rapid means of detecting of a specific portion of the genes encoding KPC and NDM production.

**Useful For:** Assessing pure isolates of gram-negative bacilli for mechanism of carbapenem resistance

**Interpretation:** This PCR detects and differentiates both blaKPC and blaNDM. A positive KPC (Klebsiella pneumoniae carbapenemase) PCR indicates that the isolate carries blaKPC. A positive NDM (New Delhi metallo-beta-lactamase) PCR indicates the isolate carries blaNDM. A negative result indicates the absence of detectable blaKPC or blaNDM DNA; however, false-negative results may occur due to inhibition of PCR, sequence variability underlying primers and, or loss of a plasmid carrying blaKPC and blaNDM.

**Reference Values:**
Not applicable

**Clinical References:**
3. CLSI Document M100-S23, Vol.33 No.1, 2013. CLSI, Wayne, PA

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**KPC (blaKPC) and NDM (blaNDM) Surveillance, PCR, Varies**

**Clinical Information:** The Centers for Disease Control and Prevention recommends active surveillance to detect unrecognized colonized patients who may be a potential source for carbapenem-resistant (drug-resistant) Enterobacteriaceae (CRE) transmission. Such surveillance testing may be focused in certain high-risk settings or patient groups (eg, ICUs, long-term acute care, patients transferred from areas or facilities with high CRE prevalence) or by infection control to investigate an outbreak. Nonsusceptibility to carbapenems in gram-negative bacilli by means of the enzyme KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) is becoming more common. The genes blaKPC and blaNDM encode KPC and NDM enzyme production, respectively. PCR is a sensitive, specific, and rapid means identifying patients colonized by CRE harboring blaKPC or blaNDM.

**Useful For:** Identifying carriers of carbapenem-resistant Enterobacteriaceae harboring KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) genes

**Interpretation:** This PCR detects and differentiates blaKPC and blaNDM in surveillance specimens (perirectal/rectal swabs or feces). A positive KPC (Klebsiella pneumoniae carbapenemase) and/or NDM (New Delhi metallo-beta-lactamase) PCR result indicates that the patient is colonized by a Gram-negative bacillus (or Gram-negative bacilli) harboring a carbapenemase gene, blaKPC and/or blaNDM, respectively. A negative result indicates the absence of detectable DNA.

**Reference Values:**
Not applicable

**Clinical References:**
3. New...

**KPND1 35207**

**KPC and NDM PCR (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**KD2T 65332**

**Krabbe Disease Second-Tier Newborn Screen, Blood Spot**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase leading to an accumulation of galactosylceramide and severe demyelination throughout the brain. Krabbe disease is primarily caused by mutations in the GALK gene, and it has an estimated frequency of 1 in 100,000 births. The clinical course of Krabbe disease can be variable, even within the same family. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease is followed by death usually by age 2. Ten percent to 15% of individuals have late onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anytime from age 6 months to the seventh decade of life. Newborn screening for Krabbe disease has recently been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Newborn screening can typically identify patients with Krabbe disease, even before onset of symptoms and also unaffected patients with GALK pseudodeficiency alleles. For these reasons, second-tier testing that includes both psychosine and 30-kb deletion analyses has been developed. Second-tier testing reduces the number of false-positive results and also limits the identification of affected individuals to patients needing immediate follow-up. Psychosine (PSY), a neurotoxin at elevated concentrations, is 1 of 4 substrates degraded by galactocerebrosidase. It has been shown to be elevated in patients with active disease and, therefore, may be a useful biomarker for the presence of disease or disease progression. The common 30-kb deletion spanning intron 10 through the end of the gene accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity alone is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second GALK mutation (with the exception of late-onset mutations) are predicted to have infantile Krabbe disease. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A (SAP-A) have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide.

**Useful For:** Second-tier testing of newborns with an abnormal screening result for Krabbe disease
Follow-up testing after an abnormal newborn screening result for Krabbe disease

**Interpretation:** An interpretive report will be provided. An elevation of psychosine is indicative of symptomatic Krabbe disease. The presence of a homozygous 30-kb deletion is indicative of early onset Krabbe disease.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Krabbe Disease, Full Gene Analysis and Large (30 kb) Deletion, Varies

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). GALC is encoded by the GALC gene located on 14q31. Krabbe disease occurs in approximately 1 in 100,000 live births with a carrier frequency of about 1 in 150 in the general population. Deficiency of GALC activity leads to an accumulation of galactosylceramide in globoid cells (multinucleated macrophages) causing severe demyelination throughout the brain. The toxic metabolite galactosylphosphatidylcholine (psychosine), an apoptotic compound, accumulates in oligodendrocytes and Schwann cells and contributes to disease pathogenicity. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration follows, with death usually occurring by age 13 months. There are later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. The clinical course of Krabbe disease can be variable even within the same family. Treatment is mostly supportive, although hematopoietic stem cell transplantation has shown some success if treatment begins before neurologic damage has occurred. The recommended first-tier test for Krabbe disease is GALCW / Galactocerebrosidase, Leukocytes. Individuals with GALC activity below the reference range for these assays are more likely to have variants in the GALC gene that are identifiable by molecular genetic testing. The above test is not reliable for detection of carriers of Krabbe disease. Additionally, measurement of the psychosine biomarker can aid in diagnosis and ongoing therapeutic monitoring (PSY / Psychosine, Blood Spot). This assay includes DNA sequencing of all 17 exons within the GALC gene as well as evaluation for the common 30-kb deletion spanning intron 10 through the end of the gene. This deletion accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second GALC alteration (with the exception of late-onset variants) are predicted to have infantile Krabbe disease. The c.857G->A (p.Gly286Asp) alteration, on the other hand, is only associated with a late-onset phenotype.

Useful For: Second-tier test for confirming a diagnosis of Krabbe disease Carrier testing for individuals with a family history of Krabbe disease in the absence of known sequence variants in the family

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

KRAS Mutation Analysis, 7 Mutation Panel, Colorectal

Clinical Information: Colorectal cancer is currently among the most common malignancies diagnosed each year. Strategies that focus on early detection and prevention effectively decrease the risk of mortality associated with the disease. In addition, an increase in survival rate for individuals with advanced stage colorectal cancer has been observed as a result of advancements in standard chemotherapeutic agents and the development of specialized targeted therapies. Monoclonal antibodies against epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, represent a new area of targeted therapy for such patients. However, studies have shown that not all individuals with colorectal cancer respond to EGFR-targeted molecules. Because the combination of targeted therapy and standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable. EGFR is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with colorectal cancer. One of the most common somatic alterations in colon cancer is the presence of activating mutations in the proto-oncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because mutant KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents such as cetuximab and panitumumab, which prevent ligand-binding to EGFR, do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of mutant KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in colon cancer is confined to patients with tumors lacking KRAS mutations. As a result, the mutation status of KRAS can be a useful marker by which patients are selected for EGFR-targeted therapy. At this time, this test is approved specifically for colorectal tumors and metastatic lesions from a colorectal primary. Refer to KRASO / KRAS Mutation Analysis, 7 Mutation Panel, Other (Non-Colorectal) for KRAS testing in noncolorectal tumors.

Useful For: Prognostic markers for cancer patients treated with epidermal growth factor receptor-targeted therapies

Interpretation: An interpretative report will be provided.

Reference Values: An interpretative report will be provided.

Clinical Information: Lung cancer is the leading cause of cancer-related deaths in the world. Non-small cell lung cancer (NSCLC) represents 70% to 85% of all lung cancer diagnoses. Randomized trials have suggested that targeted agents alone or combined with chemotherapy may be beneficial. Because the addition of targeted therapy may lead to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from targeted therapies are desirable. Monoclonal antibodies against epidermal growth factor receptor (EGFR) represent a new area of targeted therapy for such patients. However, studies have shown that not all individuals with NSCLC respond to these EGFR-targeted molecules. EGFR is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success in treating a subset of patients with NSCLC. In NSCLC, one of the most frequently reported alterations in the EGFR-signaling pathway is the presence of a mutation in the proto-oncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because mutant KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents that prevent ligand-binding to EGFR do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of mutant KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors lacking KRAS mutations. As a result, the mutation status of KRAS can be a useful marker by which patients are selected for EGFR-targeted therapy. At this time, this test is for unknown and/or unidentified primary tumors, primary tumors other than colorectal, and metastatic lesions from a primary other than colorectal. Please refer to KRASC / KRAS Mutation Analysis, 7 Mutation Panel, Colorectal for KRAS testing in colorectal tumors.

Useful For: Prognostic marker for cancer patients with noncolorectal tumors treated with epidermal growth factor receptor-targeted therapies

Interpretation: An interpretative report will be provided.

Reference Values: An interpretive report will be provided.


Lacosamide, Serum

Clinical Information: Lacosamide is approved for adjunctive therapy to treat partial-onset seizures in epileptic patients 17 years of age and older. In clinical trials, the most common side effects were dizziness, headache, nausea, and double vision. Lacosamide is completely absorbed after oral administration with negligible first-pass metabolism. Peak plasma concentrations occur 1 to 4 hours after oral dosing, and the elimination half-life is approximately 13 hours. Steady-state plasma concentrations are achieved after 3 days of twice daily repeated administration. About 40% of the administered dose is eliminated by the renal system unchanged and 30% is metabolized by hepatic isoenzymes (CYP2C9, CYP2C19, and CYP3A4) to the O-desmethyl inactive metabolite. The relationship between lacosamide plasma concentrations and its efficacy or adverse effects is not well established. However, central nervous system toxicity has been associated with higher drug concentrations in plasma.

Useful For: Monitoring serum concentrations of lacosamide to ensure compliance and appropriate dosing in specific clinical conditions (ie, severe renal impairment, mild-to-moderate hepatic impairment, and end-stage renal disease)

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical
response and may provide useful information in patients showing poor response or adverse effects, particularly when lacosamide is co-administered with other anticonvulsant drugs. Toxic ranges are not well established but occur more frequently when concentrations are greater or equal to 20 mcg/mL.

Reference Values:
Patients receiving therapeutic doses usually have lacosamide concentrations of 1.0-10.0 mcg/mL.

Clinical References:
6. McMullin M, Dalrymple R: Analysis for lacosamide in human serum by LC/MS/MS and a summary of 8,000 patient values. Ther Drug Monit. 2011;33(4):520-521

Lactate Dehydrogenase (LDH) Isoenzymes, Serum

Clinical Information: Total Lactate Dehydrogenase (LD): LD activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. As with other proteins used as tissue-function markers, the appearance of LD in the serum occurs only after prolonged hypoxia and is elevated in a number of clinical conditions including cardiorespiratory diseases, malignancy, hemolysis, and disorders of the liver, kidneys, lung, and muscle. Isoenzymes: LD is a tetrameric cytoplasmic enzyme, composed of H and M subunits. The usual designation of the isoenzyme is LD-I (H4), LD-II (H3M), LD-III (H2M2), LD-IV (HM3), and LD-V (M4). Tissue specificity is derived from the fact that tissue-specific synthesis of subunits occurs in well-defined ratios. Most notably, heart muscle cells preferentially synthesize H subunits, while liver cells synthesize M subunits nearly exclusively. Skeletal muscle also synthesizes largely M subunits so that LD-V is both a liver and skeletal muscle form of LD. The LD-I and LD-V forms are most often used to indicate heart or liver pathology, respectively. LD-I appears elevated in the serum about 24 to 48 hours after a myocardial infarction (MI), but is generally not as useful as troponin for detection of MI, unless the MI occurred at least 24 hours prior to testing. Normally, LD-II is greater than LD-I; however, when a MI has occurred, there is a "flip" in the usual ratio of LD-I/LD-II from less than 1 to greater than 1 (or at least >0.9). Use of the ratio for evaluation of patients with possible cardiovascular injury has largely been replaced by TRPS/Troponin T, 5th Generation, Plasma. The LD-V form is pronounced in patients with either primary liver disease or liver hypoxia secondary to decreased perfusion, such as occurs following an MI. However, LD-V is usually not as reliable as the transaminases (eg, aspartate aminotransferase, alanine aminotransferase) for evaluating liver function. LD-V also may be elevated in muscular damage and diseases of the skin. Although it does not appear to cause or be associated with any symptoms or particular diseases, the presence of macro-LD (LD combined with an immunoglobulin) can cause an idiosyncratic elevation of total LD.

Useful For: Investigating a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood
Differentiating heart-synthesized lactate dehydrogenase (LD) from liver and other sources
Investigating unexplained causes of LD elevations Detection of macro-LD

Interpretation: Marked elevations in lactate dehydrogenase (LD) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate-to-slight increases in LD levels are seen in myocardial infarction (MI), pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and renal disease. In liver disease, elevations of LD are not as great as the increases in aspartate aminotransferase and alanine aminotransferase. Increased levels of the enzyme...
are found in about one-third of patients with renal disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of renal disease. On occasion, a raised LD level may be the only evidence to suggest the presence of a hidden pulmonary embolus. Isoenzymes: LD-II is found in myocardium. Following a severe MI, the diagnostic ratio of LD-I divided by LD-II will change from less than 0.9 to greater than 0.9. This is referred to as an LD “flip”. LD-I elevation not due to myocardial damage may indicate hemolytic disease or other forms of in vivo hemolysis. Elevation of LD-V (least mobile isoenzyme) usually denotes liver damage. It is rarely helpful in defining skeletal muscle disease. Macro-LD can occur, which results in an elevation of LD for no clinical reason. Macro-LD greatly affects the migration of LD isoenzymes since the addition of an immunoglobulin molecule greatly retards the migration of the usual LD isoenzymes. If macro-LD is present, the electrophoretogram will show atypically migrating isoenzymes with LD activity localized near the origin.

Reference Values:

LACTATE DEHYDROGENASE (LD)

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-30 days</td>
<td>135-750 U/L</td>
</tr>
<tr>
<td>31 days-11 months</td>
<td>180-435 U/L</td>
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<tr>
<td>1-3 years</td>
<td>160-370 U/L</td>
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<td>4-6 years</td>
<td>145-345 U/L</td>
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<tr>
<td>7-9 years</td>
<td>143-290 U/L</td>
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<tr>
<td>10-12 years</td>
<td>120-293 U/L</td>
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<td>13-15 years</td>
<td>110-283 U/L</td>
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<tr>
<td>16-17 years</td>
<td>105-233 U/L</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>122-222 U/L</td>
</tr>
</tbody>
</table>

LD ISOENZYMES

I (fast band): 17.5-28.3%
II: 30.4-36.4%
III: 19.2-24.8%
IV: 9.6-15.6%
V (slow band): 5.5-12.7%


**Lactate Dehydrogenase (LDH), Body Fluid**

**Clinical Information:** Lactate dehydrogenase (LDH) activity is present in all cells of the body with the highest concentrations in the heart, liver, muscle, kidney, lung, and erythrocytes. Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end stage renal disease, and heart failure that can lead to excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Measurement of LDH in body fluids is primarily indicated to aid in the differentiation of transudative and exudative effusions as LDH activity is considered an indicator of the extent of inflammation. Dr. Richard Light derived criteria in the 1970s for patients with pleural effusions that are still used today.(2) The criteria include the measurement of total protein and LDH in pleural fluid and serum. Exudates are defined as meeting one of the following criteria: 1. Pleural fluid-to-serum protein ratio above 0.5 2. Pleural fluid LDH above two-thirds the upper limit of normal serum LDH 3. Pleural fluid-to-serum LDH ratio above 0.6 Pericardial fluid: The routine analysis of LDH to differentiate exudative and transudative pericardial effusions is not
considered helpful. (3) Peritoneal fluid: Spontaneous bacterial peritonitis or ascitic fluid infection is common (12%) at the time of admission of a patient with cirrhosis and ascites. The diagnosis is made in the presence of an elevated ascitic fluid absolute polymorphonuclear (PMN) leukocyte count (ie, >250 cells/mm$^3$) without an evident intra-abdominal, surgically treatable source of infection. (4) Secondary bacterial peritonitis (ie, ascitic fluid infection caused by a surgically treatable intra-abdominal source) can masquerade as spontaneous bacterial peritonitis. Signs and symptoms do not help separate patients who need surgical intervention from those who have spontaneous bacterial peritonitis and need only antibiotic treatment. In contrast, the initial ascitic fluid analysis and the response to treatment can assist with this important distinction. The characteristic analysis in the setting of free perforation is PMN count of 250 cells/mm$^3$ (usually many thousands) or higher, multiple organisms (frequently including fungi and enterococcus) on Gram stain and culture, and at least 2 of the following criteria: total protein above 1 g/dL, LDH above the upper limit of normal for serum, and glucose below 50 mg/dL. Studies have reported higher than 95% sensitivity but low specificity using these criteria; a computerized tomographic scan was diagnostic in 85% of patients with secondary peritonitis. (5)

**Useful For:** Identification of exudative pleural effusions
Lactate dehydrogenase in pericardial fluids is not diagnostically useful.

**Interpretation:** Pleural fluid lactate dehydrogenase (LDH) to serum LDH ratio above 0.6 are most consistent with exudative effusions. (2, 6) Peritoneal fluid LDH above 220 U/L suggests secondary, rather than spontaneous bacterial peritonitis, in conjunction with other laboratory, imaging, and clinical findings. (4, 5) Synovial fluid LDH may be elevated greater than plasma or serum LDH due to inflammatory causes. Values should be interpreted in conjunction with other clinical findings. (7) All other fluids: LDH may be used to differentiate transudative from exudative effusions. The decision limits are not well defined in fluids other than pleural fluid and should be interpreted in conjunction with other clinical findings.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**LD 8344**

**Lactate Dehydrogenase (LDH), Serum**

**Clinical Information:** Lactate dehydrogenase (LD) activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. Serum LD is elevated in a number of clinical conditions.

**Useful For:** Investigation of a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood. Monitoring changes in tumor burden after chemotherapy, although, lactate dehydrogenase elevations in patients with cancer are too erratic to be of use in the diagnosis of cancer.

**Interpretation:** Marked elevations in lactate dehydrogenase (LD) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate to slight increases in LD levels are seen in myocardial infarction.
(MI), pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and renal disease. In liver disease, elevations of LD are not as great as the increases in aspartate amino transferase (AST) and alanine aminotransferase (ALT). Increased levels of the enzyme are found in about one-third of patients with renal disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of renal disease. On occasion a raised LD level may be the only evidence to suggest the presence of a hidden pulmonary embolus.

**Reference Values:**

- 1-30 days: 135-750 U/L
- 31 days-11 months: 180-435 U/L
- 1-3 years: 160-370 U/L
- 4-6 years: 145-345 U/L
- 7-9 years: 143-290 U/L
- 10-12 years: 120-293 U/L
- 13-15 years: 110-283 U/L
- 16-17 years: 105-233 U/L
- > or =18 years: 122-222 U/L


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**LACTATE, Plasma**

**Clinical Information:** Anaerobic glycolysis markedly increases blood lactate and causes some increase in pyruvate levels, especially with prolonged exercise. The common cause for increased blood lactate and pyruvate is anoxia resulting from such conditions as shock, pneumonia, and congestive heart failure. Lactic acidosis may also occur in renal failure and leukemia. Thiamine deficiency and diabetic ketoacidosis are associated with increased levels of lactate and pyruvate. Lactate measurements that evaluate the acid-base status are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity in the blood).

**Useful For:** Diagnosing and monitoring patients with lactic acidosis

**Interpretation:** While no definitive concentration of lactate has been established for the diagnosis of lactic acidosis, lactate concentrations exceeding 5 mmol/L and pH below 7.25 are generally considered indicative of significant lactic acidosis.

**Reference Values:**

- 0-90 days (<3 months): < or =3.3 mmol/L
- 3-24 months: < or =3.1 mmol/L
- >24 months-18 years: < or =2.2 mmol/L
- >18 years: 0.5-2.2 mmol/L

**Clinical References:**


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**LACTIC ACID, Spinal Fluid**

**Clinical Information:** Anaerobic glycolysis markedly increases lactate concentrations. Lactate concentrations in cerebrospinal fluid (CSF) are increased in the presence of cerebral glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism. Lactate found in CSF is predominantly produced by central nervous system (CNS) anaerobic glycolysis and is independent of blood lactate. Lactate measurement in CSF has been proposed as a test to differentiate...
bacterial from viral meningitis.

**Useful For:** Aid in differentiating between bacterial and viral meningitis Aid in identifying increased anaerobic glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism

**Interpretation:** In addition to reference intervals, published meta-analysis of 33 studies concluded concentrations greater than 3.9 mmol/L are suggestive of bacterial meningitis, with lower concentrations suggestive of viral meningitis.(1)

**Reference Values:**
- 0-2 days: 1.1-6.7 mmol/L
- 3-10 days: 1.1-4.4 mmol/L
- 11 days-17 years: 1.1-2.8 mmol/L
- >17 years: 1.1-2.4 mmol/L


**FLACF**

**Lactoferrin, Fecal by ELISA**

**Interpretation:** A positive result is indicative of the presence of lactoferrin, a marker for fecal leukocytes. A negative result does not exclude the presence of intestinal inflammation.

**Reference Values:**
- Negative

**FLACS**

**Lactoferrin, Quantitative, Stool**

**Reference Values:**
- Less than 30.0 mcg/mL

**LACTO**

**Lactotransferrin IHC, Technical Component Only**

**Clinical Information:** Lactotransferrin (also referred to as lactoferrin) is a secreted iron-binding glycoprotein found in milk, tears, and leukocytes. It has been shown to be expressed in various tissues including tonsil, intestinal epithelium, kidney, and various regions of the brain where it is thought to play a role in iron metabolism and defense against bacteria. Lactotransferrin also plays a role in amyloidosis, specifically of the cornea, but has been observed in other tissue types.

**Useful For:** Identifying the presence of lactotransferrin in amyloid deposits An adjunct to amyloid subtyping analysis by mass spectrometry

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Ladybeetle Multicolored Asian (Harmonia axyridis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

Lamb’s Quarter, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lamb’s quarter Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
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<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
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<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

LAMB 82699

Lamb, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lamb Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


LAIHC 70499

Lambda Light Chain Immunostain, Technical Component Only

Clinical Information: Kappa or lambda immunoglobulin light chains pair with immunoglobulin heavy chains to form complete immunoglobulin molecules. These proteins serve as receptors for antigens in B lymphocytes and are the secretory products of plasma cells, forming the humoral arm of the immune system. Because individual B cells or plasma cells synthesize immunoglobulin containing...
either kappa or lambda light chains, but not both, immunoperoxidase stains for light chains can be applied to lymphocyte and plasma cell populations as a marker of clonality and B-cell lineage.

**Useful For:** A marker of B-cell and plasma cell clonality and B-cell lineage

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**LBC**

**Lamellar Body Count, Amniotic Fluid**

**Clinical Information:** Fetal lung maturity testing is used to determine the risk for developing respiratory distress syndrome (RDS) in infants born prematurely (32-39 weeks). The risk for developing RDS is inversely related to gestational age and is the most common cause of respiratory failure in neonates. RDS is associated with preterm birth due to insufficient production of pulmonary surfactant. Pulmonary surfactant is synthesized by type II pneumocytes. Surfactant consists of 90% phospholipids (primarily phosphatidylcholine and phosphatidylglycerol) and 10% proteins (surfactant proteins [SP]-A, SP-B, SP-C). Surfactant is packaged into lamellar bodies and is excreted into the alveolar space where it unravels and forms a monolayer on alveolar surfaces. Lamellar bodies can also pass into the amniotic cavity and, hence, are found in amniotic fluid. The surfactant functions to reduce the surface tension in the alveoli, preventing atelectasis. When surfactant is deficient, the small alveoli collapse and the large alveoli become overinflated and stiff, which has been associated with increased risk of developing respiratory distress. The status of fetal lung maturity is reflected in the concentration of surfactant in the form of phospholipids and lamellar bodies present in amniotic fluid. Lamellar bodies are similar in size to platelets and can be quantified on a hematology analyzer utilizing the platelet channel and used to estimate fetal lung maturity.

**Useful For:** Predicting fetal lung maturity and assessing the risk of developing neonatal respiratory distress syndrome, when performed from 32 to 39 weeks gestation

**Interpretation:** Amniotic fluid lamellar body counts (LBC) above 50,000/mcL are predictive of fetal lung maturity. Amniotic fluid LBC below 15,000/mcL are suggestive of fetal lung immaturity and increased risk of neonatal respiratory distress syndrome (RDS). The main value of fetal lung maturity testing is predicting the absence of RDS. An immature test result for fetal lung maturity is less reliable in predicting the presence of RDS.(1)

**Reference Values:**

- Immature: <15,000/mcL
- Indeterminate: 15,000-50,000/mcL
- Mature: >50,000/mcL


**Lamotrigine, Serum**

**Clinical Information:** Lamotrigine (Lamictal) is approved for therapy of bipolar I disorder and a wide variety of seizure disorders including Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and partial seizures. Its many off-label uses include treatment of migraines, trigeminal neuralgia, and treatment-refractory depression. Lamotrigine inhibits glutamate release (an excitatory amino acid) and voltage-sensitive sodium channels to stabilize neuronal membranes; it also weakly inhibits the 5-HT3 (serotonin) receptor. Lamotrigine oral bioavailability is very high (approximately 98%). The drug is metabolized by glucuronic acid conjugation to inactive metabolites. The half-life is 25 to 33 hours in adults but decreases with concurrent use of phenytoin or carbamazepine (13-14 hours) and increases with concomitant valproic acid therapy (59-70 hours), renal dysfunction, or hepatic impairment. The therapeutic range is relatively wide, 2.5 to 15 mcg/mL for most individuals. Common adverse effects are dizziness, ataxia, blurred or double vision, nausea, or vomiting.

**Useful For:** Monitoring serum concentration of lamotrigine Assessing compliance Adjusting lamotrigine dose in patients receiving other anticonvulsant drugs which interact pharmacokinetically with lamotrigine

**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response, noncompliance, or adverse effects, particularly when lamotrigine is co-administered with other anticonvulsant drugs. While most patients show response to the drug when the trough concentration is in the range of 2.5 to 15.0 mcg/mL, and show signs of toxicity when the peak serum concentration is greater than 20 mcg/mL, some patients can tolerate peak concentrations as high as 70 mcg/mL.

**Reference Values:** Patients receiving therapeutic doses usually have lamotrigine concentrations of 2.5-15.0 mcg/mL.

**Clinical References:**

**Langerin Immunostain, Technical Component Only**

**Clinical Information:** Langerhans cells are specialized antigen-presenting cells residing in the skin, usually as scattered cells along the dermal-epidermal junction. Langerin is expressed in both normal and neoplastic Langerhans cells, and is specifically associated with the assembly of Birbeck granules in these cells. Langerin positivity also has been noted in lymph node sinuses and hepatic sinusoids, in which CD1a is negative.

**Useful For:** Visualization of normal and neoplastic Langerhans cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the
context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Langust (Lobster), IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to langust (lobster) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>
LATI 70632

**LAT Immunostain, Technical Component Only**

**Clinical Information:** Linker for activation of T cells (LAT) is a transmembrane protein that plays an important role in linking engagement of the T-cell receptor (TCR) to biochemical events of T-cell activation. LAT is expressed on most T cells but is not expressed on B cells, macrophages/monocytes, dendritic cells, or epithelial cells.

**Useful For:** Distinguishing T-cell subsets and helping to classify T-cell lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**LATX 82787**

**Latex, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to latex Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with...
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<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**LDL Cholesterol, Direct**

**Interpretation:** CHD Risk Factors: +1 Age: Men, 45 years and older  
Women, 55 years and older or premature menopause without estrogen therapy +1 Family history of premature CHD +1 Current smoking +1 Hypertension +1 Diabetes mellitus +1 Low HDL Cholesterol: 39 mg/dL or less - 1 High HDL Cholesterol: 60 mg/dL or greater LDL Cholesterol: Therapeutic goal 99 mg/dL or less if CHD is present (Optional 69 mg/dL or less) 129 mg/dL or less if no CHD and two or more risk factors 159 mg/dL or less if no CHD (Circulation 2004; 110:227-39)

**Reference Values:**

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<tr>
<th>Age</th>
<th>Desirable</th>
<th>Borderline</th>
<th>Higher Risk</th>
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<tbody>
<tr>
<td>0–19 years</td>
<td>109 mg/dL or less</td>
<td>110–129 mg/dL</td>
<td>130 mg/dL or greater</td>
</tr>
<tr>
<td>20 years and older</td>
<td>129 mg/dL or less (99 mg/dL or less if patient has CHD)</td>
<td>130–159 mg/dL</td>
<td>160 mg/dL or greater</td>
</tr>
</tbody>
</table>

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**Lead Occupational Exposure, Random, Urine**

**Clinical Information:** Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy has been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the post-chelation specimen of up to 6 times the concentration in the pre-chelation specimen is normal. Blood lead is the best clinical correlation of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure due to occupational exposure in random urine specimens This test is not a substitute for blood lead screening.

**Interpretation:** Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion of more than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.
Reference Values:
Only orderable as part of profile. For more information see:
- PBUOE / Lead Occupational Exposure, Random, Urine
- HMUOE / Heavy Metal Occupational Exposure, with Reflex, Random, Urine


PBUOE
608898

Lead Occupational Exposure, Random, Urine

Clinical Information: Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy has been used as an indicator of significant lead exposure. However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." Blood lead is the best clinical correlation of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure due to occupational exposure This test is not a substitute for blood lead screening.

Interpretation: Measurements of urinary lead levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing lead body burden or long-term exposure. Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.

Reference Values:
Biological Exposure Index (BEI): <150 mcg/g creatinine


PBZP
42390

Lead Profile Occupational Exposure, Blood

Clinical Information: Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the...
ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase (ALA-D) and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Erythrocyte protoporphyrin is a biologic marker of lead toxicity. Lead inhibits several enzymes in the heme synthesis pathway and causes increased levels of RBC zinc protoporphyrin (ZPP).

**Useful For:** Detecting lead toxicity

**Interpretation:** The Centers for Disease Control and Prevention (CDC) has identified the blood lead test as the preferred test for detecting lead exposure in children. Chronic whole blood lead levels below 10 mcg/dL are often seen in children. For pediatric patients, there may be an association with blood lead values of 5 to 9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is above 25 mcg/dL in children or above 45 mcg/dL in adults. The Occupational Safety and Health Administration (OSHA) has published the following standards for employees working in industry: -Employees with whole blood lead levels above 60 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels above 50 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is below 40 mcg/dL. -All measurements assume hematocrit of 42% and are made in mcg/dL per OSHA requirements. Elevated zinc protoporphyrin (ZPP) levels in adults may indicate long-term (chronic) lead exposure or may be indicative of iron deficiency anemia or anemia of chronic disease.

**Reference Values:**

**LEAD**

All ages: 0.0-4.9 mcg/dL

Critical values

Pediatrics (< or =15 years): > or =20.0 mcg/dL

Adults (> or =16 years): > or =70.0 mcg/dL

**ZINC PROTOPORPHYRIN**

<100 mcg/dL

All measurements assume hematocrit of 42% and are made in mcg/dL per OSHA requirements.

**Lead, 24 Hour, Urine**

**Clinical Information:** Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before and after chelation therapy has been used as an indicator of lead exposure. However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." For additional information, see PBDV/Lead, Venous, with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure in 24-hour specimens This test is not a substitute for blood lead screening.

**Interpretation:** Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure. (1,2) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations. (3,4)

**Reference Values:**
- 0-17 years: not established
- > or =18 years: <2 mcg/24 hour

**Clinical References:**
older houses, old orchards, mining areas, near power plants, incinerators, landfills, and hazardous waste sites. Recent data has also shown that inexpensive cosmetic jewelry pieces sold to the general public may contain high levels of lead which can be transferred to the skin through routine handling. However, not much lead can get into your body through your skin. People may be exposed to lead by eating food or drinking water that contains lead. Drinking (tap) water in houses containing lead pipes may contain lead, especially if the water is acidic or "soft". Foods may contain small amounts of lead. Leafy fresh vegetables grown in lead-containing soils may have lead-containing dust on them. Lead may also enter foods if they are put into improperly glazed pottery or ceramic dishes and from lead-crystal glassware. However, since lead solder is no longer used in cans, very little lead is typically found in food. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is incorporated into bone (approximately 94% adults; approximately 73% children) and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Other alternative sources of lead include: moonshine distilled in lead pipes, some traditional home medicines, non-Western cosmetics (eg, surma and kohl), and some types of hair colorants, cosmetics, and dyes. Lead expresses its toxicity by several mechanisms: 1) it avidly inhibits delta-aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes involved in the synthesis of heme. In the end, this inhibition causes decreased hemoglobin synthesis resulting in anemia. 2) Lead is also an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease and may be necessary especially in children if the blood lead is higher than 45 mcg/dL. The standard chelating agents currently in use are dimeracaprol (British Anti-Lewisite, or BAL), CaNa2-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; Succimer).

**Useful For:** Detecting lead toxicity with capillary collections

**Interpretation:** No safe blood lead level in children has been identified. Lead exposure can affect nearly every system in the body. Because lead exposure often occurs with no obvious symptoms, it frequently goes unrecognized. The current reference level at which CDC recommends public health actions be initiated is 5 mcg/dL. Chelation therapy is generally initiated in children when whole blood lead concentrations are above 45 mcg/dL. OSHA has published the following standards for employees working in industry. The OSHA Standards for General Industry (CFR 1910.1025) and Construction (CFR 1926.62) apply to workers exposed to airborne lead levels 30 mcg/m(3) or greater time-weighted average and require the removal of workers if a periodic and follow-up blood lead level is 60 mcg/dL (2.9 mcmmol/L) or greater, 50 mcg/dL (2.4 mcmmol/L) or greater for construction, or the average blood lead level of all tests over a 6-month period (or if there are fewer than 3 tests over a 6-month period, the average of 3 consecutive tests) is 50 mcg/dL (2.4 mcmmol/L) or greater. Workers with a single blood lead level meeting the numerical criteria for medical removal must have their blood lead level retested within 2 weeks. If a worker is medically removed, a new blood lead level must be measured monthly during the removal period. Workers are permitted to return to work when their blood lead level is 40 mcg/dL (1.9 mcmmol/L) or less. According to the OSHA Lead Standards, a zinc protoporphyrin (ZPP) is also required on each occasion a blood lead level measurement is made.

**Reference Values:**
All ages: <5.0 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL


**Lead, Hair**

**Clinical Information:** Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

**Useful For:** Detecting lead exposure using hair specimens

**Interpretation:** Normal hair lead content is below 4.0 mcg/g. While hair lead content above 10.0 mcg/g may indicate significant lead exposure, hair is also subject to potential external contamination with environmental lead and contaminants in artificial hair treatments (e.g. dyeing, bleaching, or permanents). Ultimately, the hair lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

**Reference Values:**

<4.0 mcg/g of hair

Reference values apply to all ages.


**Lead, Nails**

**Clinical Information:** Nail analysis of lead can be used to corroborate blood analysis.

**Useful For:** Detecting lead exposure using nail specimens

**Interpretation:** Normally, the nail lead content is below 4.0 mcg/g. While nail lead content above 10.0 mcg/g may indicate significant lead exposure, nails are also subject to potential external contamination with environmental lead. Ultimately, the nail lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

**Reference Values:**

<4.0 mcg/g of nails

Reference values apply to all ages.

Lead, Venous, with Demographics, Blood

Clinical Information: Lead is a heavy metal that is naturally found in the environment that can be an acute and chronic toxin. Lead can enter the environment through releases from mining lead and other metals, and from factories that make or use lead, lead alloys, or lead compounds. Lead is released into the air during burning coal, oil, or waste. Before the use of leaded gasoline in motor vehicles was banned (January 1, 1996), most of the lead released into the U.S. environment came from vehicle exhaust. Lead was banned from household paints in 1978 but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is commonly found in soil especially near roadways, older houses, old orchards, mining areas, industrial sites, near power plants, incinerators, landfills, and hazardous waste sites. Recent data has also shown that inexpensive cosmetic jewelry pieces sold to the general public may contain high levels of lead which can be transferred to the skin through routine handling. However, not much lead can get into your body through your skin. People may be exposed to lead by eating food or drinking water that contains lead. Drinking water in houses containing lead pipes may contain lead, especially if the water is acidic or “soft”. Foods may contain small amounts of lead. Leafy fresh vegetables grown in lead-containing soils may have lead-containing dust on them. Lead may also enter foods if they are put into improperly glazed pottery or ceramic dishes and from leaded-crystal glassware. However, since lead solder is no longer used in cans, very little lead is typically found in food. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is incorporated into bone (approximately 94% adults; approximately 73% children) and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Other alternative sources of lead include: moonshine distilled in lead pipes, some traditional home medicines, non-Western cosmetics (eg, surma and kohl), and some types of hair colorants, cosmetics, and dyes. Lead expresses its toxicity by several mechanisms: 1) it avidly inhibits delta-aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes involved in the synthesis of heme. In the end, this inhibition causes decreased hemoglobin synthesis resulting in anemia. 2) Lead is also an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease and may be necessary especially in children if the blood lead is higher than 45 mcg/dL. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), CaNa2-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; Succimer).

Useful For: Detecting lead toxicity in venous blood specimens

Interpretation: No safe blood lead level in children has been identified. Lead exposure can affect nearly every system in the body. Because lead exposure often occurs with no obvious symptoms, it frequently goes unrecognized. The current reference level at which CDC recommends public health actions be initiated is 5 mcg/dL. Chelation therapy is generally indicated in children when whole blood lead concentrations are above 45 mcg/dL. OSHA has published the following standards for employees working in industry. The OSHA Standards for General Industry (CFR 1910.1025) and Construction (CFR 1926.62) apply to workers exposed to airborne lead levels 30 mcg/m(3) or greater time-weighted average and require the removal of workers if a periodic and follow-up blood level is 60 mcg/dL (2.9 mcmol/L) or greater, 50 mcg/dL (2.4 mcmol/L) or greater for construction, or the average blood lead level of all tests over a 6-month period (or if there are fewer than 3 tests over a 6-month period, the average of 3 consecutive tests) is 50 mcg/dL (2.4 mcmol/L) or greater. Workers with a single blood lead level meeting
the numerical criteria for medical removal must have their blood lead level retested within 2 weeks. If a worker is medically removed, a new blood lead level must be measured monthly during the removal period. Workers are permitted to return to work when their blood lead level is 40 mcg/dL (1.9 mcmol/L) or less. According to the OSHA Lead Standards, a zinc protoporphyrin (ZPP) is also required on each occasion a blood lead level measurement is made.

**Reference Values:**
All ages: <5.0 mcg/dL

Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

**Clinical References:**

**Lead/Creatinine Ratio, Random, Urine**

**Clinical Information:** Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." Blood lead is the best clinical correlation of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure, a toxic heavy metal, using random urine specimens

**Interpretation:** Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure.(1,2) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(3,4)

**Reference Values:**
0-17 years: not established
> or =18 years: <2 mcg/g creatinine

**Clinical References:**

**Lead/Creatinine Ratio, Urine**

**Clinical Information:** Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the postchelation specimen of up to 6 times the concentration in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure in random urine specimens

**Interpretation:** Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion greater than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

**Reference Values:**
Only orderable as part of a profile. See PBRCR / Lead/Creatinine Ratio, Random, Urine or HMCRU / Heavy Metal/Creatinine Ratio, with Reflex, Urine.


**Lead/Creatinine Ratio, Urine**

**Clinical Information:** Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the post-chelation specimen of up to 6 times the concentration in the pre-chelation specimen is normal. Blood lead is the best clinical correlation of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure using random urine specimens This test is not a substitute for blood lead screening.

**Interpretation:** Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion greater than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity. Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure.(1,2) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(3,4)

**Reference Values:**
Only orderable as part of profile. For more information see:
PBUCR / Lead/Creatinine Ratio, Random, Urine
HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

LEFLU
60292

Leflunomide Metabolite (Teriflunomide), Serum

Clinical Information: Leflunomide is a disease-modifying antirheumatic drug approved for therapy of rheumatoid arthritis and used off-label to reduce viral nephritis in renal transplant. It is a prodrug: rapid and complete metabolism converts leflunomide to its active metabolite, teriflunomide (also called A77 1726), which acts by inhibiting pyrimidine synthesis. Teriflunomide has a very long half-life, greater than 2 weeks on average. There is marked interindividual variability in leflunomide pharmacokinetics, thus therapeutic monitoring of serum teriflunomide concentrations may be helpful in optimizing therapy. Therapeutic targets remain only loosely defined and appear to vary depending on the purpose of therapy, but serum teriflunomide concentrations greater than 40 mcg/mL have been associated with better clinical outcomes. Due to the long half-life, serum specimens for therapeutic monitoring may be drawn at any point in the dosing cycle, although trough (immediately before next schedule dose) sampling is preferred for consistency. Adverse reactions to leflunomide do not correlate well with serum drug concentration, but include diarrhea, hypertension, and liver toxicity. Enhanced elimination of the drug may be required in patients who are or who wish to become pregnant, or who are experiencing toxicity; teriflunomide can persist up to 2 years after ceasing therapy unless elimination is accelerated. This can be accomplished through use of activated charcoal or a bile acid sequestrant such as cholestyramine, reducing the half-life of teriflunomide to approximately 1 day. Serum concentrations less than 0.020 mcg/mL (<20 ng/mL) on 2 independent tests at least 2 weeks apart are preferred for patients anticipating pregnancy to minimize the potential risk of teratogenesis associated with the drug.

Useful For: Therapeutic monitoring of patients actively taking leflunomide Assessment of elimination in patients requiring enhanced elimination of the drug

Interpretation: Therapy: clinical targets for serum teriflunomide (leflunomide metabolite) concentrations are still being determined, but levels greater than 40 mcg/mL appear to correlate with better outcome. Elimination: serum concentrations less than 0.020 mcg/mL (20 ng/mL) are preferred to minimize potential teratogenesis for patients considering pregnancy.

Reference Values:
Therapeutic: >40 mcg/mL
Elimination: <0.020 mcg/mL

Legionella Antigen, Random, Urine

Clinical Information: Legionnaires disease, named after the outbreak in 1976 at the American Legion convention in Philadelphia, is caused by Legionella pneumophila and is an acute febrile respiratory illness ranging in severity from mild illness to fatal pneumonia. Since that time, it has been recognized that the disease occurs in both epidemic and endemic forms, and that sporadic cases are not readily differentiated from other respiratory infections by clinical symptoms. It is estimated that about 25,000 to 100,000 Legionella infections occur annually. Known risk factors include immunosuppression, cigarette smoking, alcohol consumption, and concomitant pulmonary disease. The resulting mortality rate, which ranges up to 40% in untreated immunocompetent patients, can be lowered if the disease can be rapidly diagnosed and appropriate antimicrobial therapy instituted early. L pneumophila is estimated to be responsible for 80% to 85% of reported cases of Legionella infections with the majority of cases being caused by L pneumophila serogroup 1 alone. A variety of laboratory techniques (culture, direct fluorescent antibody, DNA probes, immunoassay, antigen detection), using a variety of specimen types (respiratory specimens, serum, urine), have been used to help diagnose Legionella pneumonia. Respiratory specimens are preferred. Unfortunately, one of the presenting signs of Legionnaires disease is the relative lack of productive sputum. This necessitates the use of invasive procedures to obtain adequate specimens (eg, bronchial washing, transtracheal aspirate, lung biopsy) in many patients. Serology may also be used but is often retrospective in nature. It was shown as early as 1979 that a specific soluble antigen was present in the urine of patients with Legionnaires disease.(1) The presence of Legionella antigen in urine makes this an ideal specimen for collection, transport, and subsequent detection in early, as well as later, stages of the disease. The antigen may be detectable in the urine as early as 3 days after onset of symptoms.

Useful For: An adjunct to culture for the presumptive diagnosis of past or current Legionnaires disease (Legionella pneumophila serogroup 1)

Interpretation: Positive Presumptive positive for Legionella pneumophila serogroup 1 antigen in urine, suggesting current or past infection. Culture is recommended to confirm infection. Negative Presumptive negative for L pneumophila serogroup 1 antigen in urine, suggesting no recent or current infection. Infection with Legionella cannot be ruled out because: -Other serogroups (other than serogroup 1, which is detected by this assay) and other Legionella species (other than L pneumophila) can cause disease -Antigen may not be present in urine in early infection -The level of antigen may be below the detection limit of the test Legionella culture is recommended for cases of suspected Legionella pneumonia due to organisms other than L pneumophila serogroup 1.

Reference Values:
Negative


Legionella Culture, Varies

Clinical Information: The Legionellaceae are ubiquitous in natural fresh water habitats, allowing them to colonize man-made water supplies, which may then serve as the source for human infections. Legionella pneumophila and the related species, Legionella bozemanii, Legionella dumoffii, Legionella gormanii, Legionella micdadei, Legionella longbeachae, and Legionella jordanis have been isolated from patients with pneumonia (Legionnaires disease). The organism has been isolated from lung tissue, bronchoalveolar lavage, pleural fluid, transtracheal aspirates, and sputum. The signs, symptoms, and radiographic findings of Legionnaires disease are generally nonspecific.
**Useful For:** Diagnosis of Legionnaires disease Because examination by rapid PCR increases sensitivity and provides faster results, Mayo Clinic Laboratories strongly recommends also ordering LEGRP / Legionella species, Molecular Detection, PCR.

**Interpretation:** Identification of Legionella species from respiratory specimens provides a definitive diagnosis of Legionnaires disease. Organisms isolated are identified as Legionella species via matrix-assisted laser desorption/ionization â€“ time of flight mass spectrometry (MALDI-TOF MS) and/or 16S rRNA gene sequencing.

**Reference Values:**
No growth

Identification of Legionella species.

**Clinical References:**

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**Legionella pneumophila (Legionnaires Disease), Antibody, Serum**

**Clinical Information:** Legionella pneumophila may cause pulmonary disease in both normal and immunocompetent hosts. The disease may occur sporadically in the form of community acquired pneumonia and in epidemics. Pneumonia (often referred to as Legionnaires disease) occurs more frequently in severely immunosuppressed individuals; a milder form of the illness, referred to as Pontiac fever, is more prevalent in normal hosts. Extrapulmonary infection with L pneumophila is rare. Legionnaires disease, Pontiac fever, and extrapulmonary infection have been collectively referred to as legionellosis. Approximately 85% of the documented cases of legionellosis have been caused by L pneumophila. Serogroups 1 and 6 of L pneumophila, by themselves, account for up to 75% of cases of legionellosis. The definitive diagnosis of L pneumophila is made by isolation of the organism on specialized culture medium (buffered charcoal yeast extract agar) or detection by a nucleic acid amplification test. In the absence of invasive procedures (eg, bronchial alveolar lavage), evaluation of patient urine samples for L pneumophila serotype 1 antigen may be useful. Testing for antibodies to L pneumophila may be helpful to establish prior exposure or infection, however, does not differentiate between acute and past infection.

**Useful For:** Evaluation of possible legionellosis (Legionnaires disease, Pontiac fever, extrapulmonary legionella infection caused by Legionella pneumophila)

**Interpretation:** A negative result indicates that IgG, IgA, and IgM antibodies to Legionella pneumophila serogroups 1-6 were not detected. Negative results do not exclude Legionella infection. It may require 4 to 8 weeks to develop a detectable antibody response; serum specimens taken early in the course of infection may not yet have significant antibody titers. Furthermore, antibody levels can fall to undetectable levels within a month of infection, early antibiotic therapy may suppress antibody response, and some individuals may not develop antibodies above detectable limits. Some culture-positive cases of Legionella do not develop Legionella antibody. Positive results are suggestive of Legionella infection. A positive result only indicates immunologic exposure at some point in time. It does not distinguish between previous or current infection. The level of antibody response may not be used to determine active infection. Other laboratory procedures or additional clinical information are necessary to establish a diagnosis. Specimens with equivocal results are retested prior to reporting. Repeat testing on a second specimen should be considered in patients with equivocal results, if clinically indicated.

**Reference Values:**

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SLEG 8122

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1537
Negative
Reference values apply to all ages.

**Clinical References:**

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**LEGRP**

**Legionella species, Molecular Detection, PCR, Varies**

**Clinical Information:** Legionnaires disease was first recognized during a pneumonia outbreak at the Legionnaires convention in Philadelphia in 1976. Investigators with the CDC isolated a novel, gram-negative bacillus, later named Legionella pneumophila. It is now widely recognized that L pneumophila (and other members of the genus Legionella) cause Legionnaires disease.

**Useful For:** Sensitive and rapid diagnosis of pneumonia caused by Legionella species The assay is not recommended as a test of cure because bacteria nucleic acids may persist after successful treatment.

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Legionella 5S rRNA gene indicates the presence of a Legionella species DNA, which may be due to Legionella infection or environmental/water Legionella DNA in the specimen. A negative PCR result indicates the absence of detectable Legionella DNA in the specimen, but does not rule-out legionellosis as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Legionella species in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

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**LEIS**

**Leishmaniasis (Visceral) Antibody, Serum**

**Clinical Information:** Visceral leishmaniasis (kala azar) is a disseminated intracellular protozoal infection that targets primarily the reticuloendothelial system (liver, spleen, bone marrow) and is caused by Leishmania donovani, Leishmania chagasi, or Leishmania infantum (L donovani complex). Transmission is by the bite of sandflies. Clinical symptoms include fever, weight loss, and splenomegaly; pancytopenia and hypergammaglobulinemia are often present. Most (90%) new cases each year arise in rural areas of India, Nepal, Bangladesh, Sudan, and Brazil, but the disease has a worldwide distribution, including the Middle East. Definitive diagnosis has required the microscopic documentation of characteristic intracellular amastigotes in stained smears from culture of aspirates of tissue (spleen, lymph node) or bone marrow. The detection of serum antibodies to the recombinant K39 antigen of L donovani is an alternative noninvasive sensitive (95%-100%) method for the diagnosis of active, visceral leishmaniasis.

**Useful For:** Aiding in the diagnosis of active visceral leishmaniasis This test should not be used as the sole criteria for diagnosis

**Interpretation:** Negative: Negative results indicate the absence of antibodies to members of the Leishmania donovoni complex. Repeat testing in 2 to 3 weeks if clinically indicated. Immunocompromised patients frequently have low or undetectable antibodies to Leishmania species.
Positive: Positive results indicate the presence of antibodies to members of the L donovoni complex, the causative agents of visceral leishmaniasis. Results should not be used as the sole criterion for diagnosis or treatment of visceral leishmaniasis and should not be used to diagnose other forms of leishmaniasis. False-positive reactions due to malaria infection have been reported.

Reference Values:
Negative
  Reference values apply to all ages.


Lemon IgG
Interpretation:
Reference Values: Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Lemon, IgE, Serum
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lemon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


**FLENG**

**Lentil IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**LEN**

**Lentil, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to lentil Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>
Lepidoglyphus destructor, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Lepidoglyphus destructor Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
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</tr>
<tr>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Leptin**

**Reference Values:**
Units: ng/mL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (BMI=22)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.7 - 5.3</td>
</tr>
<tr>
<td>Females</td>
<td>3.3 - 18.3</td>
</tr>
</tbody>
</table>

Contact laboratory for other BMI reference ranges.

---

**Leptospira, IgM, Serum**

**Clinical Information:** Leptospirosis is a zoonotic disease of worldwide prevalence, though the majority of infections occur in warm, tropical climates. Wild mammals, typically rodents, are the primary, natural reservoir for pathogenic strains of Leptospira, however, domestic animals (eg, dogs) also represent a major source of human infection. Leptospira are Gram-negative spirochetes with at least 20 different species in the genus. Of these, at least 9 species are considered pathogenic, including the most common agent of leptospirosis, Leptospira interrogans. Transmission occurs through indirect human contact (eg, via mucous membranes or abraded skin) with water, food, or soil contaminated with animal urine containing the Leptospira spirochetes. Following infection, the incubation period can range from 3 to 30 days depending on the inoculum dose and immune status of the individual. The clinical manifestations of leptospirosis can vary, ranging from a mild, flu-like illness (eg, headache, malaise, fever, arthralgia, fatigue) to fulminant disease, with severe liver and kidney involvement. The latter manifestation was previously referred to as Weil disease. Leptospira organisms may be found in the blood at the onset of disease and can persist for approximately 1 week. Subsequently, spirochetes may be found in the urine and can persist for 2 to 3 months; however, shedding may be intermittent and the numbers of organisms present may be low. While Leptospira can be grown in culture, this is a fastidious organism and requires immediate transport to the laboratory. Additionally, detectable growth requires prolonged incubation (1-6 weeks), limiting the utility of culture for acute diagnosis. For this reason, serologic detection for antibodies to Leptospira remains the method of choice for rapid diagnosis. IgM-class antibodies to this spirochete are detectable by day 6 of illness and remain detectable for 2 to 3 months following symptom onset.

**Useful For:** Aids in the diagnosis of leptospirosis

**Interpretation:** Positive: IgM antibodies to Leptospira species detected suggesting recent infection. Antibody presence alone cannot be used to definitively diagnose acute infection, as antibodies from a prior exposure or infection may remain detectable for a prolonged period of time. Borderline: Result should be interpreted with caution. Additional testing of a second, convalescent specimen is recommended. If the specimen remains borderline reactive, a second serological method should be considered if leptospirosis infection is still suspected. Negative: No IgM antibodies to Leptospira detected. Since antibodies may not be present or may be present at undetectable levels during early disease, repeat testing of a convalescent sample collected in 2 to 3 weeks is recommended.

**Reference Values:**
Negative

### Lettuce IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Lettuce, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to lettuce Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>&gt; or =100</td>
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</tbody>
</table>

Leukemia and Lymphoma Phenotyping, Technical Only,Varies

Clinical Information: Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features. This test is appropriate for hematopoietic specimens only. This is a technical only test and does not include interpretation unless reflex testing is performed. At any point, clients may request to have a Mayo Clinic hematopathologist provide an interpretation at an additional charge.

Useful For: Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia from acute myeloid leukemia (AML) Immunologic subtyping of acute leukemias Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

Interpretation: Report will include a summary of the procedure.

Reference Values:
Not applicable


Leukemia/Lymphoma Immunophenotyping, Flow Cytometry, Tissue

Clinical Information: Cellular immunophenotyping, characterizing cells by using antibodies directed against cell surface markers, is generally regarded as a fundamental element in establishing a diagnosis of tissue involvement by hematolymphoid malignancies, when used in conjunction with morphologic assessment. It is also an essential component in subclassification of hematolymphoid malignancies, when present.

Useful For: Evaluation of tissues for potential involvement by: -Chronic lymphoproliferative disorders
-Malignant lymphomas -Acute lymphoblastic leukemia -Acute myelogenous leukemia

**Interpretation:** Normal tissues typically contain a mixture of B cells with polytypic surface immunoglobulin light chain expression and T cells with unremarkable expression of the T cell-associated antigens CD3, CD5, and CD7. Typically, no appreciable blast population is present by CD45 and side scatter analysis.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Leukemia/Lymphoma Immunophenotyping, Flow Cytometry, Varies**

**Clinical Information:** Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

**Useful For:** Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

**Interpretation:** Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

**Reference Values:**
An interpretive report will be provided.
This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

**Clinical References:**
**Clinical Information:** Leukocyte adhesion deficiency syndrome type 1 (LAD-1) is an autosomal recessive disorder caused by mutations in the common chain (CD18) of the beta2-integrin family. LAD-1 is clinically characterized by recurrent infections, impaired wound healing, delayed umbilical cord separation, persistent leukocytosis, and recurrent soft tissue and oral infections. Each of the beta2-integrins is a heterodimer composed of an alpha chain (CD11a, CD11b, or CD11c) noncovalently linked to a common beta2-subunit (CD18). The alpha-beta heterodimers of the beta2-integrin family include LFA-1 (CD11a/CD18), Mac-1/CR3 (CD11b/CD18), and p150/95 (CD11c/CD18). The CD18 gene, ITGB2, and its product are required for normal expression of the alpha-beta heterodimers. Therefore, defects in CD18 expression lead to either very low or no surface membrane expression of CD11a, CD11b, and CD11c. Severe and moderate forms of LAD-1 exist, differing in the degrees of protein deficiency, which are caused by different ITGB2 mutations. Two relatively distinct clinical phenotypes of LAD-1 have been described. Patients with the severe phenotype (<1% of normal expression of CD18 on neutrophils) characteristically have delayed umbilical stump separation (>30 days), infection of the umbilical stump (omphalitis), persistent leukocytosis (>15,000/microliter) in the absence of overt active infection, and severe destructive gingivitis with periodontitis and associated tooth loss, and alveolar bone resorption. Patients with the moderate phenotype of LAD-1 (1%-30% of normal expression of CD18 on neutrophils) tend to be diagnosed later in life. Normal umbilical separation, lower risk of life-threatening infections, and longer life expectancy are common in these patients. However, leukocytosis, periodontal disease, and delayed wound healing are still very significant clinical features. Patients with LAD-1 (and other primary immunodeficiency diseases) are unlikely to remain undiagnosed in adulthood. Consequently, this test should not be typically ordered in adults for LAD-1. However, it may be also used to assess immune competence by determining CD18, CD11a, and CD11b expression.

**Useful For:** Aids in the diagnosis of leukocyte adhesion deficiency syndrome type 1, primarily in patients younger than 18 years of age CD11a, CD11b, and CD18 phenotyping

**Interpretation:** The report will include a summary interpretation of the presence or reduction in the level of expression of the individual markers (CD11a, CD11b, and CD18). Expression of the individual markers provides indirect information on the presence or absence of the CD11a/CD18 and CD11b/CD18 complexes. Specimens obtained from patients with leukocyte adhesion deficiency syndrome type 1 (LAD-1) show significant reduction (moderate phenotype) or near absence (severe phenotype) of CD18 and its associated molecules, CD11a and CD11b, on neutrophils and other leukocytes. CD11c expression also is low in LAD-1. The analytical sensitivity of the CD11c assay is insufficient to allow interpretation of CD11c surface expression. Therefore, we test only for expression of CD18, CD11a, and CD11b.

**Reference Values:**
Normal (reported as normal or absent expression for each marker)


**LECT2**

**Leukocyte Cell-Derived Chemotaxin 2 (LECT2), Immunostains Without Interpretation**

**Clinical Information:** Immunohistochemical staining for leukocyte cell-derived chemotaxin 2 (LECT2) is useful in the process of confirming amyloid subtype. Antibodies to LECT2 stain the amyloid deposits in patients with LECT2 amyloidosis. LECT2 amyloidosis typically involves the kidney, liver, and spleen.

**Useful For:** Identification and classification of amyloid subtypes in tissue

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**LTE4**

**Leukotriene E4, Urine**

**Clinical Information:** Leukotrienes (LT) are eicosanoids generated from arachidonic acid via the 5-lipoxygenase pathway. Leukotriene E4 (LTE4) is the stable end product of this pathway and, therefore, regarded as a biomarker of total cysteinyl leukotriene (cys-LT) production. Assessment of LTE4 in urine allows for noninvasive specimen collection and avoids artifactual formation of LT during phlebotomy. Generation of LTE4 occurs nonspecifically from active mast cells, basophils, eosinophils, and macrophages, and modulated through a variety of mechanisms. Elevated concentrations of LTE4 are associated with inflammatory and accelerated mast cell activation conditions, specifically in patients with systemic mast cell disease.(1) Systemic mastocytosis (SM), or systemic mast cell disease, is a myeloproliferative neoplasm that has infiltrated extracutaneous organs. Release of mast cell inflammatory mediators leads to disease symptoms including those associated with allergic and anaphylactic reactions, while increased mast cell number leads to organ dysfunction. Consensus diagnostic criteria for SM include 1 major criterion: imaging of the multifocal infiltrates; and 4 minor criteria: 1. Identifying morphological features of greater than 25% of mast cells from bone marrow

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biopsy 2. Detection of the point genetic alteration at codon 816 in the KIT gene 3. CD2 and/or CD25 expression in mast cells 4. Persistently elevated serum tryptase Diagnosis requires either 1 major plus 1 minor criterion or 3 minor criteria.(2) Measurement of urinary mast cell activation biomarkers can aid in the initial evaluation of suspected cases of systemic mast cell disease, potentially avoiding the need for imaging and bone marrow examination. Patients with SM frequently have elevated urine concentrations of LTE4,(1) N-methylhistamine,(3,4) and 2,3-dinor 11 beta-prostaglandin F2 alpha.(4) Urinary LTE4 has also demonstrated significant utility in patients with asthma and respiratory diseases. In a study of adults with mild to moderate asthma on 5-lipoxygenase inhibitors, urine LTE4 concentrations decreased approximately 40% compared with asthma control subjects, suggesting modest decreases in LTE4 production correlates with clinical improvements in asthma severity.

**Useful For:** Evaluating patients suspected of having systemic mastocytosis Identification of aspirin sensitivity in patient respiratory diagnoses

**Interpretation:** Elevated urinary leukotriene E4 (LTE4) concentrations above 104 pg/mg creatinine are consistent with the diagnosis of systemic mast cell disease when combined with clinical signs and symptoms. Pharmacological treatment with 5-lipoxygenase inhibitors or leukotriene receptor antagonists has been shown to decrease production of LTE4. Urinary LTE4 may be used together with serum tryptase, urinary 2,3-dinor 11beta-prostaglandin F2 alpha, and urinary N-methylhistamine. LTE4 values of 166 pg/mg creatinine were 89% specific for aspirin sensitivity among patients with respiratory diagnoses.

**Reference Values:**
< or =104 pg/mg creatinine

**Clinical References:**

**LEV1P**
**Level 1 Gross only (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
Reference Values:
This test is for billing purposes only.
  This is not an orderable test.

**LEV3P**  
113311  
**Level 3 Gross and microscopic (Bill Only)**

Reference Values:
This test is for billing purposes only.
  This is not an orderable test.

**LEV4P**  
113312  
**Level 4 Gross and microscopic (Bill Only)**

Reference Values:
This test is for billing purposes only.
  This is not an orderable test.

**LV4RP**  
113313  
**Level 4 Gross and Microscopic, RB (Bill Only)**

Reference Values:
This test is for billing purposes only.
  This is not an orderable test.

**LEV5P**  
113314  
**Level 5 Gross and microscopic (Bill Only)**

Reference Values:
This test is for billing purposes only.
  This is not an orderable test.

**LEV6P**  
113315  
**Level 6 Gross and microscopic (Bill Only)**

Reference Values:
This test is for billing purposes only.
  This is not an orderable test.

**LEVE**  
83140  
**Levetiracetam, Serum**

Clinical Information: Levetiracetam is approved for treatment of partial, myoclonic, and tonic-clonic seizures, and is used off-label for manic states and migraine prophylaxis. Levetiracetam has very favorable pharmacokinetics with good bioavailability and rapid achievement of steady state. Its hepatic metabolism is minimal and nonoxidative, making it safe for use with hepatic enzyme inducers or inhibitors. The major metabolite is a carboxylic acid derivate, which is inactive and accounts for roughly one quarter of the administered dose. Levetiracetam is excreted renally, with a mean half-life of 7 hours in adults and slightly less than that in children. Renal dysfunction may warrant therapeutic monitoring and/or dose adjustment. Given the lack of drug interactions and favorably pharmacokinetics, the primary uses for therapeutic drug monitoring of levetiracetam are compliance assurance and management of physiological changes such as puberty, pregnancy, and aging. Toxicities associated with levetiracetam use include decreased hematocrit and red blood cell count, decreased neutrophil count, somnolence, asthenia, and dizziness. These toxicities may be associated with blood concentrations in the therapeutic range.

Useful For: Monitoring serum concentration of levetiracetam, particularly in patients with renal
**Interpretation:** Most individuals display optimal response to levetiracetam with serum levels 10.0 to 40.0 mcg/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Toxic levels have not been well established. Therapeutic ranges are based on specimen collected at trough (ie, immediately before the next dose).

**Reference Values:**
10.0-40.0 mcg/mL

**Clinical References:**

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**Lidocaine, Serum**

**Clinical Information:** Lidocaine is commonly used as a local anesthetic, but it is also effective at controlling ventricular arrhythmia and ventricular fibrillation in children and adults. For cardiac therapy, optimal therapeutic response is seen when serum concentrations are between 1.5 and 5.0 mcg/mL. Lidocaine is protein-bound (60-80%), primarily to alpha-1-acid glycoprotein; concentrations of this protein increase after myocardial infarction, which may decrease the amount of free lidocaine and, thus, its efficacy. Lidocaine undergoes extensive first-pass hepatic metabolism and, therefore, is not administered orally. It is eliminated via renal clearance, with a half-life of approximately 1.5 to 2 hours. Diseases that reduce hepatic or renal function reduce clearance and prolong elimination of lidocaine. Toxicity occurs when the serum concentration of lidocaine is greater than 6.0 mcg/mL and is usually associated with symptoms of central nervous system excitation, light-headedness, confusion, dizziness, tinnitus, and blurred or double vision. This can be accompanied by bradycardia and hypotension leading to cardiovascular collapse.

**Useful For:** Assessing optimal lidocaine dosing during the acute management of ventricular arrhythmias following myocardial infarction or during cardiac manipulation such as surgery Assessing potential lidocaine toxicity

**Interpretation:** Optimal response to lidocaine occurs when the serum concentration is between 1.5 and 5.0 mcg/mL. Toxicity is more likely when concentrations exceed 6.0 mcg/mL.

**Reference Values:**
Therapeutic: 1.5-5.0 mcg/mL
Critical value: >6.0 mcg/mL

**Clinical References:**

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**LIM Domain Only 2 (LMO2) Immunostain, Technical Component Only**

**Clinical Information:** LIM domain only 2 (LMO2) is a transcription factor that regulates vascular and hematopoietic systems and is involved in hematolymphoid neoplasia. LMO2 is preferentially expressed by germinal center B cells and may also be expressed in erythroid and myeloid precursors and in megakaryocytes. Expression has been observed in cases of lymphoblastic and acute myeloid leukemia.
It is rarely expressed in mature T, natural killer, and plasma cell neoplasms and is absent from nonhematolymphoid tissues except for endothelial cells. In the diagnosis of B-cell lymphomas, LMO2 can be useful in an immunohistochemical panel to assign a germinal center phenotype.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Lime, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to lime. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:


### Limited Bleeding Diathesis Profile Interpretation

**Clinical Information:** Bleeding problems may be associated with a wide variety of coagulation abnormalities or may be due to problems not associated with coagulation (trauma and surgery as obvious examples). A partial listing of causes follows. -Deficiency or functional abnormality (congenital or acquired) of any of the following coagulation proteins: fibrinogen (factor I), factor II (prothrombin), factor V, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia C; bleeding severity not always proportionate to factor level), factor XIII (fibrin-stabilizing factor), von Willebrand factor (VWF antigen and activity), and alpha-2 plasmin inhibitor and plasminogen activator inhibitor (PAI-I; severe deficiency in rare cases). Neither alpha-2 plasmin inhibitor nor PAI-I are included as a routine bleeding diathesis assay component, but either can be performed if indicated or requested. -Deficiency (thrombocytopenia) or functional abnormality of platelets such as congenital (eg, Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disorders) and acquired (eg, myeloproliferative disorders, uremia, drugs) disorders. Platelet function abnormalities cannot be studied on mailed-in specimens. -Specific factor inhibitors (most commonly directed against factor VIII); factor inhibitors occur in 10% to 15% of the hemophilia population and are more commonly associated with severe deficiencies of factor VIII or IX (antigen <1%). The inhibitor appears in response to transfusion therapy with factor concentrates with no correlation of occurrence and amount of therapy. Factor VIII inhibitors may occur spontaneously in the postpartum patient, with certain malignancies, in association with autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), in the elderly, and for no apparent reason. -Other acquired causes of increased bleeding include paraproteinemia; other factor-specific inhibitors, including those against factor V, factor XI; or virtually any of the coagulation proteins. -Acute disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), which is a fairly common cause of bleeding. Bleeding can also occur in patients with chronic ICF.

**Useful For:** Detection of the more common potential causes of abnormal bleeding (eg, factor deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors) and a simple screen to evaluate for an inhibitor or severe deficiency of factor XIII (rare). This test is not useful for assessing platelet function (eg, congenital or acquired disorders such as Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disease, myeloproliferative disease, associated platelet dysfunction), which requires fresh platelets

**Interpretation:** An interpretive report will be provided.

**Reference Values:**

Only orderable as part of a profile. For more information see ALBLD / Bleeding Diathesis Profile,
Limited, Plasma.

An interpretive report will be provided.


**FLALA**

57193

**Limulus Amebocyte Lysate (Endotoxin)**

**Clinical Information:** The LAL is used as a quantitative test to detect gram-negative endotoxin in aqueous solutions used in patient management. The LAL assay is not recommended for serum or plasma samples due to the presence of inhibitory factors. It is essential to maintain specimen sterility and prevent false positive results from exogenous gram negative bacteria.

**Reference Values:**

<table>
<thead>
<tr>
<th>LEVEL DETECTED</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.05 EU/mL</td>
<td>None Detected</td>
</tr>
<tr>
<td>0.125 EU/mL</td>
<td>Action level for dialysis water</td>
</tr>
<tr>
<td>&lt;0.25 EU/mL</td>
<td>Maximum allowable level for dialysis water and USP acceptable limits for injectable or irrigation water</td>
</tr>
<tr>
<td>0.25 EU/mL</td>
<td>Action level for dialysis fluid</td>
</tr>
<tr>
<td>&lt;0.50 EU/mL</td>
<td>Maximum allowable level for dialysis fluid and USP acceptable limits for inhalatory water.</td>
</tr>
<tr>
<td>2.00 EU/mL</td>
<td>Acceptable upper limit for Hemodialysis reuse water.</td>
</tr>
</tbody>
</table>

**LIND**

82862

**Linden, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to linden Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<thead>
<tr>
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<tr>
<td>0</td>
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<td>Positive</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
### Linseed, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to linseed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>≥100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Lipase, Body Fluid

Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids and produce fatty acids and 2-acylglycerol. The pancreas is the primary source of serum lipase. Pancreatic injury results in increased serum lipase levels. Serum lipase is measured to aid in the diagnosis of pancreatitis. Peritoneal fluid: The digestive enzymes amylase and lipase can be measured in the identification of pancreatic fluid in the peritoneal cavity. Concentrations are expected to be elevated and at least several-fold times higher in fluid of pancreatic origin compared to simultaneous concentrations in serum. Drain fluid: Lipase is expected to be elevated in drain fluids formed due to chronic pancreatitis or formation of a fistula following surgery. Comparison to serum concentrations is recommended with elevations several-fold higher than blood being suggestive of the presence of pancreatic fluid in the drained cavity.

Useful For: Determining whether pancreatic inflammation or pancreatic fistula may be contributing to a pathological accumulation of fluid.

Interpretation: Fluids (peritoneal, drain): Lipase concentrations several-fold higher than serum lipase concentrations is suggestive of the presence of pancreatic fluid in the drained cavity. All other fluids: Body fluid lipase activity may become elevated due to the presence of pancreatic fluid in the drained cavity. Results should be interpreted in conjunction with serum lipase and other clinical findings.

Reference Values: An interpretive report will be provided.


Lipase, Random Urine

Reference Values: Adult: ≤ 4 U/L

Lipase, Serum

Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids and produce fatty acids and 2-acylglycerol. Bile salts and a cofactor, colipase, are required for full catalytic activity and greatest specificity. The pancreas is the primary source of serum lipase. Both lipase and colipase are synthesized in the pancreatic acinar cells and secreted by the pancreas in roughly equimolar amounts. Lipase is filtered and reabsorbed by the kidneys. Pancreatic injury results in increased serum lipase levels.

Useful For: Investigating pancreatic disorders, usually pancreatitis.
Interpretation: In pancreatitis, lipase becomes elevated at about the same time as amylase (4-8 hours). But lipase may rise to a greater extent and remain elevated much longer (7-10 days) than amylase. Elevations 2 to 50 times the upper reference have been reported. The increase in serum lipase is not necessarily proportional to the severity of the attack. Normalization is not necessarily a sign of resolution. In acute pancreatitis, normoamylasemia may occur in up to 20% of such patients. Likewise, the existence of hyperlipemia may cause a spurious normoamylasemia. For these reasons, it is suggested that the 2 assays complement and not exclude each other, and that both enzymes should be assayed.

Reference Values:
13-60 U/L


BFLA1

Lipid Analysis, Body Fluid

Clinical Information: Measurement of cholesterol and triglycerides combined with detection of chylomicrons in body fluids is useful for diagnosing chylous effusion or differentiating from pseudochylous effusion.(1) Chylous effusions are characterized by the presence of chyle which contains chylomicrons circulating through the lymphatic system. Pseudochylous effusions do not have chylomicrons. Cholesterol concentrations in serous effusions increase over time due to chronic exudative processes that cause cell lysis or increased vascular permeability. These fluids have a milky appearance can be confused with chylous effusions. While chylous effusions often have elevated triglyceride concentrations and decreased cholesterol concentrations, identification of chylomicrons is considered the gold standard for the diagnosis. Pleural Fluid: Chylothorax is the name given to pleural effusions containing chylomicrons. They develop when chyle accumulates from disruption of the lymphatic system, often the thoracic duct, caused mainly by malignancy or trauma.(1) Lymph contains chylomicron rich chyle characterized by high concentrations of triglycerides. Pseudochylous effusions are the name given to milky appearing effusions that do not contain lymphatic contents but rather form gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema and by definition the effluent contains high concentrations of cholesterol.(2) Differentiation of pseudochylothorax from chylothorax is important as their milky or opalescent appearance is similar, however therapeutic management strategies differ. Peritoneal Fluid: Chylous ascites is the name given to peritoneal effusions containing chylomicrons. Obstruction of lymph flow causing leakage from dilated subserosal lymphatics, exudation through the walls of retroperitoneal megalymphatics, and direct leakage of chyle due to a lymphoperitoneal fistula have been proposed as possible mechanisms causing chylous ascites.(3) Elevated triglyceride concentrations have the best correlation with detection of chylomicrons, while cholesterol is not useful at predicting the presence or absence of chylomicrons.

Useful For: Distinguishing between chylous and nonchylous effusions

Interpretation: Pleural fluid cholesterol concentrations 46 to 65 mg/dL are consistent with exudative effusions. Cholesterol concentrations >200 mg/dL suggest pseudochylous effusion. Triglyceride concentrations >110 mg/dL are consistent with chylous effusions. Triglyceride concentrations <50 mg/dL are usually not due to chylous effusions. Fluid: Peritoneal Peritoneal fluid triglyceride concentrations >187 mg/dL are most consistent with chylous effusion. Cholesterol concentrations 33 to 70 mg/dL suggest malignant causes of ascites.

Reference Values:
An interpretive report will be provided.

Clinical Panel, Fasting, Serum

Clinical Information: Cardiovascular disease is the number one cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually, many in individuals who have no prior symptoms. Prevention of ischemic cardiovascular events is key. Risk factors including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, are used by physicians to identify individuals likely to have an ischemic event.

Useful For: Evaluation of cardiovascular risk

Interpretation: Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Clinic Laboratories reports (see Reference Values). Lipids are most commonly measured to assess cardiovascular risk. Maintaining desirable concentrations of lipids lowers the risk of heart attacks or strokes. Establishing appropriate treatment strategies and lipid goals require the results for each component of a lipid profile be considered in context with other risk factors including, age, sex, smoking status, family and personal history of heart disease.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

TOTAL CHOLESTEROL
Desirable: <200 mg/dL
Borderline high: 200-239 mg/dL
High: > or =240 mg/dL

TRIGLYCERIDES
Normal: <150 mg/dL
Borderline high: 150-199 mg/dL
High: 200-499 mg/dL
Very high: > or =500 mg/dL

HDL CHOLESTEROL
Males
> or =40 mg/dL
Females
> or =50 mg/dL

LDL CHOLESTEROL
Desirable: <100 mg/dL
Above desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

NON-HDL CHOLESTEROL
Desirable: <130 mg/dL
Above desirable: 130-159 mg/dL
Borderline high: 160-189 mg/dL  
High: 190-219  
Very high: > or =220 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17:

**TOTAL CHOLESTEROL**  
Acceptable: <170 mg/dL  
Borderline high: 170-199 mg/dL  
High: > or =200 mg/dL

**TRIGLYCERIDES**  
2-9 years:  
Acceptable: <75 mg/dL  
Borderline high: 75-99 mg/dL  
High: > or =100 mg/dL  
10-17 years:  
Acceptable: <90 mg/dL  
Borderline high: 90-129 mg/dL  
High: > or =130 mg/dL

**HDL CHOLESTEROL**  
Low HDL: <40 mg/dL  
Borderline low: 40-45 mg/dL  
Acceptable: >45 mg/dL

**LDL CHOLESTEROL**  
Acceptable: <110 mg/dL  
Borderline high: 110-129 mg/dL  
High: > or =130 mg/dL

**NON-HDL CHOLESTEROL**  
Acceptable: <120 mg/dL  
Borderline high: 120-144 mg/dL  
High: > or =145 mg/dL


Lipid Panel, Non-Fasting, Serum

Clinical Information: Cardiovascular disease is the number one cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually, many in individuals who have no prior symptoms. Prevention of ischemic cardiovascular events is key. Risk factors, including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, are used by physicians to identify individuals likely to have an ischemic event.

Useful For: Evaluation of cardiovascular risk

Interpretation: Mayo Clinic has adopted the National Lipid Association classifications, which are
Lipids are most commonly measured to assess cardiovascular risk. Maintaining desirable concentrations of lipids lowers the risk of heart attacks or strokes. Establishing appropriate treatment strategies and lipid goals require the results for each component of a lipid profile to be considered in context with other risk factors including, age, sex, smoking status, family and personal history of heart disease. Nonfasting lipids are endorsed by the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, in which a follow-up fasting sample is recommended if triglycerides exceed normal levels.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Goal for Adults 18 and up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL CHOLESTEROL</strong></td>
<td></td>
</tr>
<tr>
<td>Desirable</td>
<td>&lt;200 mg/dL</td>
</tr>
<tr>
<td>Borderline high</td>
<td>200-239 mg/dL</td>
</tr>
<tr>
<td>High</td>
<td>&gt; or =240 mg/dL</td>
</tr>
<tr>
<td><strong>TRIGLYCERIDES</strong></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>&lt;200 mg/dL</td>
</tr>
<tr>
<td>Females</td>
<td>&lt;175 mg/dL</td>
</tr>
<tr>
<td><strong>HDL CHOLESTEROL</strong></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>&gt; or =40 mg/dL</td>
</tr>
<tr>
<td>Females</td>
<td>&gt; or =50 mg/dL</td>
</tr>
<tr>
<td><strong>LDL CHOLESTEROL</strong></td>
<td></td>
</tr>
<tr>
<td>Desirable</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Above desirable</td>
<td>100-129 mg/dL</td>
</tr>
<tr>
<td>Borderline high</td>
<td>130-159 mg/dL</td>
</tr>
<tr>
<td>High</td>
<td>160-189 mg/dL</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt; or =190 mg/dL</td>
</tr>
<tr>
<td><strong>NON HDL CHOLESTEROL</strong></td>
<td></td>
</tr>
<tr>
<td>Desirable</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Above desirable</td>
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<td>Very high</td>
<td>&gt; or =220 mg/dL</td>
</tr>
</tbody>
</table>

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17 years of age:

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Goal for Ages 2-17 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL CHOLESTEROL</strong></td>
<td></td>
</tr>
<tr>
<td>Acceptable</td>
<td>&lt;170 mg/dL</td>
</tr>
<tr>
<td>Borderline high</td>
<td>170-199 mg/dL</td>
</tr>
<tr>
<td>High</td>
<td>&gt; or =200 mg/dL</td>
</tr>
<tr>
<td><strong>TRIGLYCERIDES</strong></td>
<td></td>
</tr>
<tr>
<td>2-9 years:</td>
<td></td>
</tr>
<tr>
<td>Acceptable</td>
<td>&lt;75 mg/dL</td>
</tr>
<tr>
<td>Borderline high</td>
<td>75-99 mg/dL</td>
</tr>
</tbody>
</table>
High: > or =100mg/dL
10-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL

HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline low: 40-45 mg/dL
Acceptable: >45 mg/dL

LDL CHOLESTEROL
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

NON HDL CHOLESTEROL
Acceptable: <120 mg/dL
Borderline high: 120-144 mg/dL
High: > or =145 mg/dL


LRBA
608113

Lipopolysaccharide-Responsive Beige-Like Anchor Protein (LRBA) Deficiency, Blood

Clinical Information: Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency is a rare autosomal recessive primary immunodeficiency disease (PID) caused by homozygous or compound heterozygous loss-of-function variants in the LRBA gene. It has a wide spectrum of clinical manifestations, including immune dysregulation and autoimmunity, inflammatory bowel disease (IBD), early-onset hypogammaglobulinemia, recurrent infections and organomegaly.

Useful For: Aids in the diagnosis of lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency This test is not useful for identifying a carrier status for LRBA deficiency.

Interpretation: The results are reported as the percentage and MFI (mean fluorescence intensity) of lipopolysaccharide-responsive beige-like anchor protein (LRBA) expression in T cells and B cells. The majority of genetically confirmed cases of LRBA deficiency lead to the absence of LRBA expression. Therefore, the lack of LRBA expression in T and B cells is consistent with LRBA deficiency. In this case, genetic analysis of LRBA to confirm the diagnosis and to identify the underlying variant will be recommended. In addition, there are reported cases of LRBA deficiency where the protein is expressed but at lower intensity. Therefore, the expression of LRBA at diminished intensity could be due to a pathogenic LRBA variant, which would have to be confirmed or ruled out by genetic and functional analysis.

Reference Values: The appropriate reference values will be provided on the report.


**LPAWS 89005**

**Lipoprotein (a) Cholesterol, Serum**

**Clinical Information:** Lipoprotein (a) (Lp[a]) consists of an LDL particle that is covalently bound to an additional protein, apolipoprotein (a) (apo[a]). Apo (a) has high-sequence homology with the coagulation factor plasminogen and, like LDL, Lp(a) contains apolipoprotein B100 (apoB). Thus, Lp(a) is both proatherogenic and prothrombotic. Lp(a) is an independent risk factor for coronary heart disease (CHD), ischemic stroke, and aortic valve stenosis. Lp(a) has been referred to as "the most atherogenic lipoprotein." The mechanism of increased risk is unclear but most likely involves progression of atherosclerotic stenosis via intimal deposition of cholesterol and promotion of thrombosis via homology to plasminogen. Concentrations of Lp(a) particles in the blood can be expressed readily by 2 methods: as concentrations of Lp(a) protein or as Lp(a) cholesterol. Mayo Clinic’s Cardiovascular Laboratory Medicine measures and reports Lp(a) cholesterol individually (LPAWS / Lipoprotein [a] Cholesterol, Serum) and as a part of the lipoprotein profile (LMPP / Lipoprotein Metabolism Profile, Serum). The cholesterol content of Lp(a) particles varies little, and Lp(a) can contain significant proportions of the serum cholesterol. Lp(a) is a highly heterogeneous particle mainly because of the variable number of kringles repeats in the apo(a) portion of the molecule. Kringles are specific structural domains containing 3 intra-strand disulfide bonds that are highly homologous to similar repeats found in plasminogen. In the clinical laboratory, immunologic methods are generally used to quantify Lp(a) protein mass. Reagents for Lp(a) mass measurement are available from multiple manufacturers and although standardization efforts are underway, currently available methods are not standardized. Difficulties in standardizing Lp(a) mass measurement arise from the variability in signals produced by different reagents due to the size polymorphisms of apo(a). For this reason, some elevations of Lp(a) mass are associated with low levels of Lp(a) cholesterol. Lp(a) quantification can be done by densitometric measurement of Lp(a) cholesterol. This method measures only the cholesterol contained in the Lp(a) particles and is thus not influenced by the relative size of the apo(a) particle. Because Lp(a) cholesterol measurement is not influenced by apo(a) size, it may provide a more specific assessment of cardiovascular risk than Lp(a) mass measurement. Lp(a) cholesterol measurement may be used in concert with Lp(a) mass determination or may be used as a stand-alone test for assessment of risk.

**Useful For:** Evaluation of increased risk for cardiovascular disease and events: -Most appropriately measured in individuals at intermediate risk for cardiovascular disease -Patients with early atherosclerosis or strong family history of early atherosclerosis without explanation by traditional risk factors should also be considered for testing -Follow-up evaluation of patients with elevations in lipoprotein (a) mass

**Interpretation:** Increased lipoprotein (a) (Lp[a]) cholesterol has been associated with increased risk for the development of atherothrombotic disease. Aggressive LDL reduction is the recommended treatment approach in most patients with increased Lp(a). Patients with increased Lp(a) cholesterol values have an approximate 2-fold increased risk for developing cardiovascular disease events. Lipoprotein-X (LpX) is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice, and is an indicator of cholestasis. The presence of LpX will be reported if noted during Lp(a) cholesterol analysis.

**Reference Values:**
Lp(a) CHOLESTEROL
Normal: <5 mg/dL
LpX
Undetectable


**Lipoprotein (a), Serum**

**Clinical Information:** Lipoprotein (a) (Lp[a]) consists of an LDL particle that is covalently bound to an additional protein, apolipoprotein (a) (Apo[a]). Apo(a) has high-sequence homology with the coagulation factor plasminogen and, like LDL, Lp(a) contains apolipoprotein B100 (ApoB). Thus, Lp(a) is both proatherogenic and prothrombotic. Lp(a) is an independent risk factor for coronary heart disease (CHD), ischemic stroke, and aortic valve stenosis. Lp(a) has been referred to as “the most atherogenic lipoprotein.” The mechanism of increased risk is unclear but, most likely, involves progression of atherosclerotic stenosis via intimal deposition of cholesterol and promotion of thrombosis via homology to plasminogen. Concentrations of Lp(a) particles in the blood can be expressed readily by 2 methods: as concentrations of Lp(a) protein or as Lp(a) cholesterol. Mayo's Cardiovascular Laboratory Medicine measures and reports Lp(a) cholesterol individually (LPAWS / Lipoprotein [a] Cholesterol, Serum) and as a part of the lipoprotein profile (LMPP / Lipoprotein Metabolism Profile). The cholesterol content of Lp(a) particles varies little, and Lp(a) can contain significant proportions of the serum cholesterol. Unlike Lp(a) cholesterol, accurate immunochemical measurement of Lp(a)-specific protein is complicated by the heterogeneity of Lp(a) molecular size. Due to the large number of genetic alterations in the population, any given individual can have an Apo(a) protein between 240 to 800 kDa. This heterogeneity leads to inaccuracies when results are expressed in terms of mg/dL of protein. In addition, the degree of atherogenicity of the Lp(a) particle may depend on the molecular size of the Lp(a)-specific protein. Serum concentrations of Lp(a) are related to genetic factors and are largely unaffected by diet, exercise, and lipid-lowering pharmaceuticals. However, in a patient with additional modifiable CHD risk factors, more aggressive therapy to normalize these factors may be indicated if the Lp(a) value is also increased.

**Useful For:** Cardiovascular disease (CVD) risk refinement in patients with moderate or high risk based on conventional risk factors. This test is not recommended as a screening test in the healthy population.

**Interpretation:** The frequency distribution of serum lipoprotein (a) (Lp[a]) concentrations is markedly skewed toward the low end, with approximately 85% of the population having concentrations below 30 mg/dL. Lp(a) concentrations above 30 mg/dL are associated with 2- to 3-fold increased risk of cardiovascular events independent of conventional risk markers.

**Reference Values:**
< or =30 mg/dL
Values >30 mg/dL may suggest increased risk of coronary heart disease.

Lipoprotein Metabolism Profile, Serum

Clinical Information: Lipoprotein metabolism profile analysis adds practical information about the etiology of cholesterol and/or triglyceride elevation. In some patients, increased serum lipids reflect elevated levels of intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), lipoprotein a (Lp[a]), or even the abnormal lipoprotein complex-LpX. These elevations can be indicative of a genetic deficiency in lipid metabolism or transport, nephrotic syndrome, endocrine dysfunction or even cholestasis. Identification of the lipoprotein associated with lipid elevation is achieved using the gold-standard methods, which include ultracentrifugation, selective precipitation, electrophoresis, and direct measurement of cholesterol and triglycerides in isolated lipoprotein fractions. Proper characterization of a patient's dyslipidemic phenotype aids clinical decisions and guides appropriate therapy. Classifying the hyperlipoproteinemia into phenotypes places disorders that affect plasma lipid and lipoprotein concentrations into convenient groups for evaluation and treatment. A clear distinction must be made between primary (inherited) and secondary (liver disease, alcoholism, metabolic diseases) causes of dyslipoproteinemia. Lipoprotein profiling will identify the presence of Lp(a) and LpX and distinguish between the following dyslipidemias: -Exogenous hyperlipemia (Type I) -Familial hypercholesterolemia (Type IIa) -Familial combined hyperlipidemia (Type IIb) -Familial dysbetalipoproteinemia (Type III) -Endogenous hyperlipemia (Type IV) -Mixed hyperlipemia (Type V)

Useful For: Diagnosing dyslipoproteinemia Quantitation of cholesterol and triglycerides in very-low-density lipoprotein (VLDL), LDL, HDL, and chylomicrons Identification of LpX Classifying hyperlipoproteinemias (lipoprotein phenotyping) Evaluating patients with abnormal lipid values (cholesterol, triglyceride, HDL, LDL) Quantifying lipoprotein a (Lp[a]) cholesterol

Interpretation: For discussion of primary disorders associated with dyslipidemias see Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions. Patients with increased Lp(a) cholesterol values have been associated with increased risk for the development of atherothrombotic disease. Aggressive LDL reduction is the recommended treatment approach in most patients with increased Lp(a). Lipoprotein-X (LpX) is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice, and is an indicator of cholestasis. The presence of LpX will be reported if noted during Lp(a) cholesterol analysis.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>LDL Cholesterol (mg/dL)</th>
<th>LDL Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-9 years</td>
<td>* Acceptable: high: 170-199 High: &gt; or =200</td>
<td>* Acceptable: high: 75-99 * Acceptable: high: 90-129 High: &gt; or =100</td>
<td>* Acceptable: high: 110-129 High: &gt; or =130</td>
<td>&lt; or = 50</td>
</tr>
<tr>
<td>10-17 years</td>
<td>** Desirable: high: 200-239 High: &gt; or = 240</td>
<td>** Normal: high: 150-199 High: 200-499 Very high: &gt; or =500</td>
<td>*** Desirable: Desirable: 100-129 Borderline high: 130-159 High: 160-189 Very high: &gt; or =190</td>
<td>&lt; or = 50</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Apolipoprotein B (mg/dL)

<table>
<thead>
<tr>
<th>Category</th>
<th>Acceptable</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>high: 90-109</td>
<td>&gt; or =110</td>
</tr>
</tbody>
</table>

### HDL Cholesterol (mg/dL)

<table>
<thead>
<tr>
<th>Category</th>
<th>Low: low: 40-45</th>
<th>Acceptable: &gt; 45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>*** Low: 90-99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*** High: &gt; or =110</td>
</tr>
</tbody>
</table>

### VLDL Cholesterol (mg/dL)

**Reference Values:** have not been established for patients that are of age. *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents**

### LDL Triglycerides (mg/dL)

**Reference Values:** have not been established for patients that are of age. *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents**

### Chylomicron Cholesterol

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

### Chylomicron Triglycerides

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

### Lp(a) cholesterol

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable</td>
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</table>

### LpX

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

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**Clinical References:**


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**FLISD**

**Lisdexamfetamine as Metabolite, Urine**

**Reference Values:** Reporting limit determined each analysis.

None Detected ng/mL

**LITH**

**Lithium, Serum**

**Clinical Information:** Lithium alters the intraneuronal metabolism of catecholamines by an unknown mechanism. It is used to suppress the manic phase of manic-depressive psychosis. Lithium is distributed throughout the total water spaces of the body and is excreted primarily by the kidney. Toxicity from lithium salts leads to ataxia, slurred speech, and confusion. Since the concentration of lithium in the serum
varies with the time after the dose, blood for lithium determination should be drawn at a standard time, preferably 8 to 12 hours after the last dose (trough values).

**Useful For:** Monitoring therapy of patients with bipolar disorders, including recurrent episodes of mania and depression Evaluating lithium toxicity

**Interpretation:** The therapeutic range for lithium has been established at 0.5 to 1.2 mmol/L. Within this range, most people will respond to the drug without symptoms of toxicity. However, response and side effects are individual. Lithium concentrations and side effects can increase with the loss of salt and water from the body, which can occur with a salt-free diet, excessive sweating, or an illness that causes vomiting and diarrhea. A variety of prescribed drugs, over-the-counter medications, and supplements can also increase, decrease, or interfere with the concentrations of lithium.

**Reference Values:**
Therapeutic: 0.5-1.2 mmol/L (trough concentration)
Critical value: >1.6 mmol/L
There is no relationship between peak concentration and degree of intoxication.

**Clinical References:**

**Liver Fatty Acid-Binding Protein (L-FABP) Immunostain, Technical Component Only**

**Clinical Information:** Liver fatty acid-binding protein (L-FABP) is a cytoplasmic protein that binds free fatty acids and their coenzyme A derivative, bilirubin, and other hydrophobic ligands. It may have roles in lipid transport, uptake, and metabolism. L-FABP can be used with a panel of immunohistochemical markers (beta-catenin, glutamine synthetase, C-reactive protein, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. L-FABP is downregulated in type 1 adenomas, but is expressed in normal liver and other adenoma types.

**Useful For:** Classification of hepatic adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Liver Profile, Serum

Clinical Information: The hepatic function panel may be used to help diagnose liver disease if a person has signs and symptoms that indicate possible liver dysfunction. If a person has a known condition or liver disease, testing may be performed at intervals to monitor the health of the liver and to evaluate the effectiveness of any treatments. Abnormal tests on a liver panel may prompt a repeat analysis of one or more tests, or of the whole panel, to see if the elevations or decreases persist and may indicate the need for additional testing to determine the cause of the liver dysfunction.

Useful For: Screening for liver damage, especially if someone has a condition or is taking a drug that may affect the liver.

Interpretation: Hepatic function panel results are not diagnostic of a specific condition; they indicate that there may be a problem with the liver. In a person who does not have symptoms or identifiable risk factors, abnormal liver test results may indicate a temporary liver injury or reflect something that is happening elsewhere in the body—such as in the skeletal muscles, pancreas, or heart. It may also indicate early liver disease and the need for further testing and periodic monitoring. Results of liver panels are usually evaluated together. Several sets of results from tests performed over a few days or weeks are often assessed together to determine if a pattern is present. Each person will have a unique set of test results that will typically change over time. A healthcare practitioner evaluates the combination of liver test results to gain clues about the underlying condition. Often, further testing is necessary to determine what is causing the liver damage or disease.

Reference Values:

TOTAL BILIRUBIN
0-6 days: Refer to http://bilitool.org/ for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: <15.0 mg/dL
15 days to 17 years: < or =1.0 mg/dL
>18 years: < or =1.2 mg/dL

DIRECT BILIRUBIN
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are under 12 months of age.

ASPARTATE AMINOTRANSFERASE
Males
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

ALANINE AMINOTRANSFERASE
Males
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are under 12 months of age.

Females
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are under 12 months of age.

ALKALINE PHOSPHATASE
Males
4 years: 149-369 U/L
5 years: 179-416 U/L
6 years: 179-417 U/L
7 years: 172-405 U/L
8 years: 169-401 U/L
9 years: 175-411 U/L
10 years: 191-435 U/L
11 years: 185-507 U/L
12 years: 185-562 U/L
13 years: 182-587 U/L
14 years: 166-571 U/L
15 years: 138-511 U/L
16 years: 102-417 U/L
17 years: 69-311 U/L
18 years: 52-222 U/L
> or =19 years: 45-115 U/L

Females
4 years: 169-372 U/L
5 years: 162-355 U/L
6 years: 169-370 U/L
7 years: 183-402 U/L
8 years: 199-440 U/L
9 years: 212-468 U/L
10 years: 215-476 U/L
11 years: 178-526 U/L
12 years: 133-485 U/L
13 years: 120-449 U/L
14 years: 153-362 U/L
15 years: 75-274 U/L
16 years: 61-264 U/L
17-23 years: 52-144 U/L
24-45 years: 37-98 U/L
46-50 years: 39-100 U/L
51-55 years: 41-108 U/L
56-60 years: 46-118 U/L
61-65 years: 50-130 U/L
> or =66 years: 55-142 U/L
Reference values have not been established for patients who are under 4 years of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are under 12 months of age.

TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are under 12 months of age.


Liver/Kidney Microsome Type 1 Antibodies, Serum

Clinical Information: Autoimmune liver disease (eg, autoimmune hepatitis and primary biliary cirrhosis) is characterized by the presence of autoantibodies including smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA), and anti-liver/kidney microsomal antibodies type 1 (anti-LKM-1).(1) Subtypes of autoimmune hepatitis (AIH) are based on autoantibody reactivity patterns. Anti-LKM-1 antibodies serve as a serologic marker for AIH type 2 and typically occur in the absence of SMA and antinuclear antibodies. These antibodies react with a short linear sequence of the...
recombinant antigen cytochrome monooxygenase P450 2D6. Patients with AIH type 2 more often tend to be young, female, and have severe disease that responds well to immunosuppressive therapy.

**Useful For:** Evaluation of patients with liver disease of unknown etiology Evaluation of patients with suspected autoimmune hepatitis

**Interpretation:** Seropositivity for anti-liver/kidney microsomal antibodies type 1 (anti-LKM-1) antibodies is consistent with a diagnosis of autoimmune hepatitis (AIH) type 2.

**Reference Values:**
- < or =20.0 Units (negative)
- 20.1-24.9 Units (equivocal)
- > or =25.0 Units (positive)

Reference values apply to all ages.

**Clinical References:**

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**Lobster, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to lobster Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Locust Black (Robinia pseudoacacia) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

**Long QT Syndrome Multi-Gene Panel, Blood**

**Clinical Information:** Long QT syndrome (LQTS) is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on electrocardiogram (EKG), which may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. RWS has an estimated prevalence of 1 in 3,000 individuals. Of the families who meet clinical diagnostic criteria for RWS, approximately 75% have known genetic causes, while approximately 25% have no detectable pathogenic variants in any of the genes known to cause RWS. Approximately 3% of RWS cases are the result of large deletions or duplications in KCNQ1 or KCNH2. Deletions/duplications have not been reported in the other genes implicated in RWS. Only about half of the individuals with a pathogenic gene variant associated with RWS have symptoms, usually one to a few syncopal spells, and thus many patients with this condition unfortunately present with sudden cardiac death as their first symptom. Cardiac events may occur any time from infancy through adulthood, but are most common from the preteen years through the 20s. Additionally, RWS is believed to account for approximately 10% to 15% of sudden infant death syndrome (SIDS) cases. In some cases, LQTS may be associated with congenital profound bilateral sensorineural hearing loss, known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either KCNQ1 or KCNE1. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies that may include hand/foot syndactyly, structural heart defects, facial dysmorphism, and neurodevelopmental features. Ventricular tachyarrhythmia is the leading cause of death with an average age of death of 2.5 years. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the CACNA1C gene. Management strategies for LQTS include pharmacologic therapies, implantable cardioverter defibrillators (ICD), or other surgical interventions, and lifestyle restrictions such as avoidance of competitive sports or other triggers for cardiac events. In some cases, knowledge of the LQTS genotype may assist in tailoring an individual treatment plan. For example, patients with an SCN5A pathogenic variant may not respond well to the typical first-line therapy of beta-blockers and may have a lower threshold for consideration of an ICD. Genetic testing in LQTS is recommended and supported by multiple consensus statements to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death and, thus, EKG analysis alone is insufficient to rule out the diagnosis and genetic testing is necessary to confirm the presence or absence of disease in at-risk family members. Pre- and posttest genetic counseling is an important factor in the diagnosis and management of LQTS and is supported by expert consensus statements.

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of long QT syndrome (LQTS) Establishing a diagnosis of a LQTS, in some cases,
allowing for appropriate management and surveillance for disease features based on the gene involved.

Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### LORAZ
**Lorazepam (Ativan), Serum**

**Reference Values:**
Reference Range: 50.0 - 240.0 ng/mL

### NRHDL
**Low-Density Lipoprotein (LDL) a-High Density Cholesterol, Serum**

**Reference Values:**
Only orderable as part of a profile. For more information see LDLD / Low-Density Lipoprotein (LDL) Cholesterol (Beta-Quantification), Serum.

### LDLD
**Low-Density Lipoprotein (LDL) Cholesterol (Beta-Quantification), Serum**

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 1570
**Clinical Information:** Low-density lipoprotein cholesterol (LDL-C) is widely recognized as an established cardiovascular risk marker predicated on results from numerous clinical trials that demonstrate the ability of LDL-C to independently predict development and progression of coronary heart disease. In the United States, LDL-C remains the primary focus for cardiovascular risk assessment and evaluation of pharmacologic effectiveness. There have been considerable educational efforts invested and directed towards physicians, laboratorians, allied health staff, and the general public regarding LDL-C and strategies to lower LDL-C for reduction of cardiovascular risk. Low-density lipoproteins are a heterogeneous population of lipid particles classically defined as having a density of 1.006 to 1.063 kg/L obtained by preparative ultracentrifugation. The gold standard beta-quantification (beta-quant or BQ) method combines ultracentrifugation with precipitation and yields a collective quantitative measurement of LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and lipoprotein(a) (Lp[a]) cholesterol. In practice, LDL-C is most commonly reported using the Friedewald equation (LDL-C=TC-HDL-TG/5). Importantly, there are significant shortcomings and limitations to the Friedewald equation. Calculated LDL-C is not accurate in patients who are nonfasting, have triglycerides greater than 400 mg/dL, or have type III hyperlipoproteinemia. The equation is particularly inaccurate once the triglycerides are above 200 mg/dL or when LDL-C is <70 mg/dL. Extremely low concentrations of LDL-C are associated with 2 genetic disorders; abetalipoproteinemia and hypobetalipoproteinemia. In both cases individuals will have very low total cholesterol and diminished or absent LDL-C, apolipoprotein B (apoB) (APLB / Apolipoprotein B, Plasma) and very low-density lipoprotein cholesterol (VLDL-C). Patients may exhibit clinical signs and symptoms of polyneuropathy, intestinal fat malabsorption, hepatosteatosis, and fat soluble vitamin deficiencies (VAE / Vitamin A and Vitamin E, Serum).

**Useful For:** Evaluation of cardiovascular risk Assessment of low-density lipoprotein C (LDL-C) in patients with hypertriglyceridemia, type III hyperlipoproteinemia/dysbetalipoproteinemia, or when an accurate gold standard determination of LDL-C is required Diagnosis of familial hypobetalipoproteinemia and abetalipoproteinemia

**Interpretation:** The optimal concentration for LDL cholesterol in primary prevention depends on individual patient risk. Risk factors include: family history of coronary heart disease (CHD), hypertension, cigarette smoking, obesity, diabetes mellitus, and low HDL cholesterol, among others. Consideration of drug treatment is recommended for patients with LDL cholesterol >190 mg/dL. Values <80 mg/dL indicate hypobetalipoproteinemia. Complications due to fat malabsorption may be present in affected individuals. Undetectable LDL-C is highly suggestive of abetalipoproteinemia. Related polyneuropathy may exist in affected individuals.

**Reference Values:**

The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for LDL-C in adults (ages 18 years and up):

- Desirable: <100 mg/dL
- Above Desirable: 100-129 mg/dL
- Borderline high: 130-159 mg/dL
- High: 160-189 mg/dL
- Very high: > or =190 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for LDL-C in children and adolescents (ages 2-17 years):

- Acceptable: <110 mg/dL
- Borderline high: 110-129 mg/dL
- High: > or =130 mg/dL

**Low-Grade Fibromyxoid Sarcoma (LGFMS), 16p11.2 (FUS or TLS) Rearrangement, FISH, Tissue**

**Clinical Information:** Low-grade fibromyxoid sarcoma (LGFMS) is a rare malignant soft tissue tumor characterized by a bland fibroblastic spindle cell proliferation arranged in alternating fibrous and myxoid areas, with or without giant collagen rosettes. These tumors are characterized by the chromosome translocation t(7;16)(q33-34;p11), which results in the fusion of FUS (also called TLS) on chromosome 16 to CREB3L2 (also called BBF2H7) on chromosome 7. Greater than 70% of LGFMS are cytogenetically characterized by this translocation. In rare cases, a variant t(11;16)(p11;p11) has been described in which FUS is fused to CREB3L1 (OASIS), a gene structurally related to CREB3L2. Testing of FUS locus rearrangement should be concomitant with histologic evaluation, and positive results may support the diagnosis of LGFMS.

**Useful For:** Supporting the diagnosis of low-grade fibromyxoid sarcoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FUS probe set. A positive result is consistent with the diagnosis of low-grade fibromyxoid sarcoma (LGFMS). A negative result suggests that a FUS gene rearrangement is not present, but does not exclude the diagnosis of LGFMS.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
1. Fletcher CDM, Unni K, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC: Lyon 2002, pp 104-105

**Loxapine (Loxitaner) and 8-Hydroxyloxapine**

**Reference Values:**
Loxapine:
- Reference Range: 5.0 - 30.0 ng/mL

8-Hydroxy-Loxapine:
- Reference Range: 20.0 - 100.0 ng/mL

**LSD Trace Analysis, Urine**

**Reference Values:**
Reporting limit determined each analysis.
- None Detected ng/mL
- No reference data available

**Lung Cancer Rearrangement Testing, Tumor**
**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common rearrangements (fusions) involving 4 genes known to be associated with lung cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. See Activated/Partner Gene Breakpoints Resulting in Targeted Fusion Transcripts Interrogated by Lung Panel in Special Instructions for details regarding the targeted gene regions evaluated by this test.

**Useful For:** Identifying lung tumors that may respond to targeted therapies by simultaneously assessing multiple genes involved in rearrangements resulting in fusion transcripts Diagnosis and management of patients with lung cancer This test is not intended for use for hematological malignancies.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**Lung Cancer, ALK (2p23) Rearrangement, FISH, Tissue**

**Clinical Information:** Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung carcinoma (NSCLC) accounts for 75% to 80% of all lung cancers with an overall 5-year survival rate of 10% to 15%. Standard chemotherapy regimens have had marginal success in improving clinical outcomes. Targeted treatments may be used as novel molecular changes are identified. Rearrangements of the anaplastic lymphoma kinase (ALK) locus are found in a subset of lung carcinomas and their identification may guide important therapeutic decisions for the management of these tumors. The fusion of echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene results from an inversion of chromosome band 2p23. The ALK-EML4 rearrangement has been identified in 3% to 5% of NSCLC with the majority in adenocarcinoma and younger male patients who were light or nonsmokers. Lung cancers harboring ALK rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors, but may be highly sensitive to ALK inhibitors, like Xalkori (crizotinib). The drug Xalkori works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that Xalkori treatment of patients with tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression.

**Useful For:** Identifying patients with late-stage, non-small cell lung cancers who may benefit from treatment with the drug Xalkori.

**Interpretation:** A positive result (ALK rearrangement identified) is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result suggests rearrangement of the ALK locus and a tumor that may be responsive to ALK inhibitor therapy. A negative result suggests no rearrangement of the ALK gene region at 2p23. A specimen is considered positive if >50% demonstrate a signal pattern consistent with an ALK rearrangement and considered negative if <10% of cells are positive. If the results are equivocal (>10% and <50%), an additional 50...
cells are scored and would be considered positive if >15% of cells exhibit a signal pattern consistent with an ALK rearrangement and negative if <15% of cells exhibit an ALK rearrangement.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Lung Cancer, RET (10q11) Rearrangement, FISH, Tissue

Clinical Information: Lung cancer is the leading cause of cancer mortality in developed countries. The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK rearrangements and EGFR mutations, respectively. Abnormalities of the RET proto-oncogene at chromosome 10q11 have been identified as the causative genetic abnormality in the neoplasia predisposition syndrome multiple endocrine neoplasia type II (MEN2), as well as in thyroid carcinomas. Recently, chromosomal rearrangements of RET have been identified in a subset of lung adenocarcinomas. Patients with tumors harboring RET rearrangements may benefit from RET kinase inhibitors, but the clinical benefits of the inhibitor has not yet been clarified.

Useful For: Identifying RET gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for EGFR mutations and ALK rearrangements

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the RET locus and a tumor that may be responsive to RET kinase inhibitor therapy. A negative result suggests no rearrangement of the RET gene region at 10q11.

Reference Values: An interpretive report will be provided.


Lung Cancer, ROS1 (6q22) Rearrangement, FISH, Tissue

Clinical Information: Lung cancer is the leading cause of cancer mortality in developed countries. The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK rearrangements and EGFR mutations, respectively. The c-ros oncogene 1 (ROS1), originally described in glioblastomas, has been identified as a potential relevant therapeutic target in lung adenocarcinoma. Crizotinib has shown in vitro activity and early evidence of clinical activity in ROS1-rearranged tumors.

Useful For: Identifying c-ros oncogene 1 (ROS1) gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds...
the normal cutoff for the probe set. A positive result suggests rearrangement of the ROS1 locus and a tumor that may be responsive to ALK-inhibitor therapy. A positive result suggests rearrangement of the c-ros oncogene 1 (ROS1) locus and a tumor that may be responsive to anaplastic lymphoma kinase (ALK)-inhibitor therapy.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Lung Cancer-Targeted Gene Panel with Rearrangement, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes known to be associated with response or resistance to specific targeted therapies. This is a single assay that uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations and rearrangements (fusions) involving 11 genes known to be associated with lung cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. See Targeted Gene Regions Interrogated by Lung Panel and Activated/Partner Gene Breakpoints Resulting in Targeted Fusion Transcripts Interrogated by Lung Panel in Special Instructions for details regarding the targeted gene regions evaluated by this test.

**Useful For:** Identifying lung tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously in EGFR, BRAF, KRAS, HRAS, NRAS, ALK, ERBB2, MET, ALK, ROS1, RET, and NTRK1 genes Diagnosis and management of patients with lung cancer This test is not intended for use for hematological malignancies.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**LUNGP 65144**

**Lung Cancer-Targeted Gene Panel, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations in 8 genes known to be associated with lung cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. See Targeted Gene Regions Interrogated by Lung Panel in Special Instructions for details regarding the targeted gene regions evaluated by this test.

**Useful For:** Identifying lung tumors that may respond to targeted therapies by assessing multiple gene targets within the EGFR, BRAF, KRAS, HRAS, NRAS, ALK, ERBB2, and MET genes simultaneously Diagnosis and management of patients with lung cancer This test is not intended for use for hematological malignancies.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**LUPN 82613**

**Lupin, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for...
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to lupin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Lupus Anticoagulant Evaluation with Reflex**

**Reference Values:**

Lupus Anticoagulant Not Detected

This interpretation is based on the following test results:

- PTT-LA Screen $< 40$ seconds
- DRVVT Screen $< 45$ seconds

**Lupus Anticoagulant Profile Interpretation**

**Clinical Information:** Lupus anticoagulant (LAC) is an antibody to negatively charged phospholipid that interferes with phospholipid-dependent coagulation tests.Â LAC is found in, but not limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune disorders and collagen vascular disease, and occurs in response to medications or certain infections (e.g., respiratory tract...
infections in children) and in individuals with no obvious underlying disease. LAC has been associated
with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II
deficiency associated with LAC may be at risk for bleeding.

**Useful For:** Confirming or excluding the presence of lupus anticoagulant (LAC), distinguishing LAC
from specific coagulation factor inhibitors and nonspecific inhibitors. Investigating a prolonged
activated thromboplastin time, especially when combined with other coagulation studies. This test is not
useful for the detection of antiphospholipid antibodies that do not affect coagulation tests. We
recommend separate testing for serum phospholipid (cardiolipin) antibodies.

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as a reflex. For more information see ALUPP / Lupus Anticoagulant Profile, Plasma.

An interpretive report will be provided.

**Clinical References:**
1. Arnout J, Vermeylen J: Current status and implications of autoimmune
2002 March 7;346(10):752-763 3. Proven A, Bartlett RP, Moder KG et al: Clinical importance of
positive tests for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc

**Lupus Anticoagulant Profile Technical Interpretation**

**Clinical Information:** Lupus anticoagulant (LAC) is an antibody to negatively charged
phospholipid that interferes with phospholipid-dependent coagulation tests. LAC is found in, but not
limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune
disorders and collagen vascular disease, occurs in response to medications or certain infections (eg,
respiratory tract infections in children), and in individuals with no obvious underlying disease. LAC has
been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia
or factor II deficiency associated with LAC may be at risk for bleeding.

**Useful For:** Confirming or excluding the presence of lupus anticoagulant (LAC). Distinguishing LAC
from specific coagulation factor inhibitors and nonspecific inhibitors. Investigating a prolonged
activated thromboplastin time, especially when combined with other coagulation studies. This test is not
useful for the detection of antiphospholipid antibodies that do not affect coagulation tests. We
recommend separate testing for serum phospholipid (cardiolipin) antibodies.

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as a reflex. For more information see ALUPP / Lupus Anticoagulant Profile, Plasma.

An interpretive report will be provided.

**Clinical References:**
1. Arnout J, Vermeylen J: Current status and implications of autoimmune
2002 March 7;346(10):752-763 3. Proven A, Bartlett RP, Moder KG et al: Clinical importance of
Apr;79(4):467-475
phospholipid that interferes with phospholipid-dependent coagulation tests. LAC is found in, but not limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune disorders and collagen vascular disease, and occurs in response to medications or certain infections (e.g., respiratory tract infections in children) and in individuals with no obvious underlying disease. LAC has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LAC may be at risk for bleeding.

Useful For: Confirming or excluding the presence of lupus anticoagulant (LAC), distinguishing LAC from specific coagulation factor inhibitors and nonspecific inhibitors Investigating a prolonged activated thromboplastin time, especially when combined with other coagulation studies This test is not useful for the detection of antiphospholipid antibodies that do not affect coagulation tests. We recommend separate testing for serum phospholipid (cardiolipin) antibodies.

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values: An interpretive report will be provided.


Luteinizing Hormone (LH) Beta Immunostain, Technical Component Only

Clinical Information: In males, luteinizing hormone (LH) stimulates androgen production by Leydig cells in the testis. In females, LH stimulates androgen and progesterone synthesis in ovarian follicles and corpus luteum, and promotes ovulation. A sparse population of cells (approximately 10%) stain positively in normal pituitary gland. This population of gonadotrophs also produces follicle-stimulating hormone. Immunohistochemical detection of LH beta may be useful in the classification of pituitary adenomas.

Useful For: Classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Luteinizing Hormone (LH), Pediatrics, Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). LH is produced by the anterior pituitary gland under regulation of the hypothalamic gonadotropin releasing hormone (GnRH) and feedback from gonadal steroid hormones. In children, LH, along with follicle-stimulating hormone (FSH), is used to diagnose precocious (early) and delayed puberty. Precocious puberty refers to the appearance of physical and
hormonal signs of pubertal development at an earlier age than is considered normal (before 8 years of age in girls and 9 years of age in boys). Evaluation of precocious puberty includes measurement of LH and FSH to determine whether gonadotropins are increased in relation to chronologic age (gonadotropin-dependent) or whether sex steroid secretion is occurring independent of LH and FSH (gonadotropin-independent). In gonadotropin-dependent precocious puberty, basal LH levels are often elevated into the pubertal range and show a pubertal (heightened) response to GnRH stimulation. In gonadotropin-independent precocious puberty, the LH level is low at baseline and fails to respond to GnRH stimulation. Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics by age 14 years in boys and by age 12 years in girls. Delayed puberty usually results from inadequate gonadal steroid secretion that, in turn, is most often caused by a defective gonadotropin secretion from the anterior pituitary, due to defective production of GnRH from the hypothalamus. Random measurements of LH and FSH, together with estradiol (females) or testosterone (males), are useful to distinguish between primary and secondary causes of delayed puberty.

**Useful For:** Diagnosis of precocious puberty and delayed puberty in children

**Interpretation:** In young children, high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), along with the development of secondary sexual characteristics at an unusually young age, are an indication of gonadotropin-dependent precocious puberty (also called central precocious puberty). Prepubertal levels of LH and FSH in children exhibiting some signs of pubertal changes may be an indication of gonadotropin-independent precocious puberty (also refer as precocious pseudopuberty). In precocious pseudopuberty the signs and symptoms are the result of elevated levels of estrogen in girls or testosterone in boys. In delayed puberty, LH and FSH levels can be normal or below what is expected for a youth within this age range. The test for LH response to gonadotropin releasing hormone in addition to other testing may help to diagnose the reason for the delayed puberty.

**Reference Values:**

**Females**
- <1 year: <0.02-18.3 IU/L
- 1-8 years: <0.02-0.3 IU/L
- 9-10 years: <0.02-4.8 IU/L
- 11-13 years: <0.02-11.7 IU/L
- 14-17 years: <0.02-16.7 IU/L

**Tanner Stages**
- Stage I (1-8 years): <0.02-0.3 IU/L
- Stage II: <0.02-4.1 IU/L
- Stage III: 0.6-7.2 IU/L
- Stage IV-V: 0.9-13.3 IU/L

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

**Males**
- <1 year: <0.02-5.0 IU/L
- 1-8 years: <0.02-0.5 IU/L
- 9-10 years: <0.02-3.6 IU/L
- 11-13 years: 0.1-5.7 IU/L
- 14-17 years: 0.8-8.7 IU/L

**Tanner Stages**
- Stage I (1-8 years): <0.02-0.5 IU/L
- Stage II: 0.03-3.7 IU/L
- Stage III: 0.09-4.2 IU/L
- Stage IV-V: 1.3-9.8 IU/L

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.
Luteinizing Hormone (LH), Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 non-covalently bound subunits (alpha and beta). The alpha subunit of LH, follicle-stimulating hormone (FSH), thyrotropin (formerly known as thyroid-stimulating hormone: TSH), and human chorionic gonadotropin (hCG) are identical and contain 92 amino acids. The beta subunits of these hormones vary and confer the hormones' specificity. LH has a beta subunit of 121 amino acids and is responsible for interaction with the LH receptor. This beta subunit contains the same amino acids in sequence as the beta subunit of hCG, and both stimulate the same receptor; however, the hCG-beta subunit contains an additional 24 amino acids, and the hormones differ in the composition of their sugar moieties.

Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, FSH, and LH, from the anterior pituitary. In both males and females, LH is essential for reproduction. In females, the menstrual cycle is divided by a midcycle surge of both LH and FSH into a follicular phase and a luteal phase. This "LH surge" triggers ovulation thereby not only releasing the egg, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first 2 weeks. In case of pregnancy, luteal function will be further maintained by the action of hCG (a hormone very similar to LH) from the newly established pregnancy. LH supports thecal cells in the ovary that provide androgens and hormonal precursors for estradiol production. LH in males acts on testicular interstitial cells of Leydig to cause increased synthesis of testosterone.

Useful For: An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

Interpretation: In both males and females, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Postmenopausal LH levels are generally above 40 IU/L. FSH and LH are generally elevated in: - Primary gonadal failure - Complete testicular feminization syndrome - Precocious puberty (either idiopathic or secondary to a central nervous system lesion) - Menopause - Primary ovarian hypofunction in females - Polycystic ovary disease in females - Primary hypogonadism in males LH is decreased in: - Primary ovarian hyperfunction in females - Primary hypergonadism in males FSH and LH are both decreased in failure of the pituitary or hypothalamus.

Reference Values:
Males
< or =4 weeks: Not established
>1 month-< or =12 months: < or =0.4 IU/L
>12 months-< or =6 years: < or =1.3 IU/L
>6-< or =11 years: < or =1.4 IU/L
>11-< or =14 years: 0.1-7.8 IU/L
>14-< or =18 years: 1.3-9.8 IU/L
>18 years: 1.3-9.6 IU/L

Females
< or =4 weeks: Not established
>1-< or =12 months: < or =0.4 IU/L
>12 months-< or =6 years: < or =0.5 IU/L
>6-< or =11 years: < or =3.1 IU/L
>11-< or =14 years: < or =11.9 IU/L
>14-< or =18 years: 0.5-41.7 IU/L
Premenopausal:
- Follicular: 1.9-14.6 IU/L
- Midcycle: 12.2-118.0 IU/L
- Luteal: 0.7-12.9 IU/L
- Postmenopausal: 5.3-65.4 IU/L

**Clinical References:**

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**Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid**

**Clinical Information:** Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex. Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia garinii are the primary causes of Lyme disease in Europe and parts of Asia. Lyme disease is the most commonly reported tick-borne infection in North America and Europe, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, cardiac disease, and neurological disease may be later stage manifestations. Neuroinvasive Lyme disease (NLD) can affect either the peripheral or central nervous system, with patients classically presenting with the triad of lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis, which can affect the motor or sensory nerves, or both. These symptoms can occur in any combination or alone. Some patients may present with Bannwarth syndrome, which includes painful radiculoneuritis with variable motor weakness. NLD should be considered in individuals presenting with appropriate symptoms who have had exposure to ticks in a Lyme endemic region of the United States, Europe or Asia. Patients meeting these criteria should be evaluated for the presence of anti-Bbsl antibodies in serum using the standard 2-tiered testing algorithm (LYME / Lyme Disease Serology, Serum) as recommended by the Centers for Disease Control and Prevention. Briefly, the LYME test includes testing of serum specimens by an anti-Bbsl antibody enzyme-linked immunosorbent assay (ELISA), followed by supplemental testing of all reactive samples using an immunoblot or western blot for detection of IgM- and IgG-class antibodies to Bbsl. Notably, the majority of patients with NLD will be seropositive in serum. Therefore, it is recommended that all patients tested by this assay also have LYME / Lyme Disease Serology, Serum performed. Results from these assays, alongside appropriate exposure history and clinical presentation, may be used to establish a diagnosis of NLD. Spinal fluid (CSF) should not be tested for the presence of antibodies to Bbsl using the current 2-tiered testing algorithm as there are no interpretive criteria for assessment of anti-Bbsl IgM and IgG immunoblot banding patterns in CSF. Additionally, while the presence of antibodies to Bbsl in CSF may be due to true intrathecal antibody synthesis, thus indicating central nervous system (CNS) infection, antibodies may alternatively be present as a result of passive diffusion through the blood-brain barrier or due to blood contamination of CSF during a traumatic lumbar puncture. The Lyme CNS infection antibody index (AI) is performed as a reflex and quantitatively measures the level of anti-Bbsl antibodies in CSF and serum, ideally collected within 24 hours of each other, and normalizes those levels to total IgG and albumin in both specimen sources. A positive Lyme CNS AI indicates true intrathecal antibody synthesis of antibodies to Bbsl, which alongside clinical and exposure history can be used to establish a diagnosis of NLD.

**Useful For:** Aiding in the diagnosis of neuroinvasive Lyme disease or neuroborreliosis due to Borrelia species associated with Lyme disease (eg, Borrelia burgdorferi, Borrelia garinii, Borrelia afzelii)
**Interpretation:** Negative: No antibodies to Lyme disease causing Borrelia species detected in spinal fluid. A negative result in a patient with appropriate exposure history and symptoms consistent with neuroinvasive Lyme disease should not be used to exclude infection. Testing for antibodies to Lyme disease-causing Borrelia species in serum should be performed. Reactive: Supplemental testing to determine a Lyme central nervous system antibody index has been ordered. Diagnosis of neuroinvasive Lyme disease should not be established solely based on a reactive screening result.

**Reference Values:**

Reference values apply to all ages.

**Clinical References:**


**Lyme Central Nervous System Infection IgG, Antibody Index, Spinal Fluid**

**Clinical Information:** Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex. Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia garinii are the primary causes of Lyme disease in Europe and parts of Asia. Lyme disease is the most commonly reported tick-borne infection in North America and Europe, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, cardiac disease, and neurological disease may be later stage manifestations. Neuroinvasive Lyme disease (NLD) can affect either the peripheral or central nervous system, with patients classically presenting with the triad of lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis, which can affect the motor or sensory nerves, or both. These symptoms can occur in any combination or alone. Some patients may present with Bannwarth syndrome, which includes painful radiculoneuritis with variable motor weakness. NLD should be considered in individuals presenting with appropriate symptoms who have had exposure to ticks in a Lyme endemic region of the United States, Europe or Asia. Patients meeting these criteria should be evaluated for the presence of anti-Bbsl antibodies in serum using the standard 2-tiered testing algorithm (LYME / Lyme Disease Serology, Serum) as recommended by the Centers for Disease Control and Prevention. Briefly, the STTTA includes testing of serum specimens by an anti-Bbsl antibody enzyme-linked immunosorbent assay (ELISA), followed by supplemental testing of all reactive samples using an immunoblot or western blot for detection of IgM- and IgG-class antibodies to Bbsl. Notably, the majority of patients with NLD, more than 99%, will be seropositive in serum. This alongside appropriate exposure history and clinical presentation may be used to establish a diagnosis of NLD. Cerebrospinal fluid (CSF) may also be tested for the presence of antibodies to Bbsl using the current 2-tiered testing algorithm as defined for serum samples. However, there are currently no interpretive criteria for assessment of anti-Bbsl IgM and IgG immunoblot banding patterns in CSF. Additionally, while the presence of antibodies to Bbsl in CSF may be due to true intrathecal antibody synthesis, thus indicating central nervous system (CNS) infection, antibodies may alternatively be present as a result of passive diffusion through the blood-brain barrier or due to blood contamination of CSF during a traumatic lumbar
puncture. The Lyme CNS antibody index (AI) quantitatively measures the level of anti-Bbsl antibodies in CSF and serum, ideally collected within 24 hours of each other, and normalizes those levels to total IgG and albumin in both specimen sources. A positive Lyme CNS AI indicates true intrathecal antibody synthesis of antibodies to Bbsl, which alongside clinical and exposure history can be used to establish a diagnosis of NLD.

**Useful For:** Providing antibody index information to aid in the diagnosis of neuroinvasive Lyme disease or neuroborreliosis due to Borrelia species associated with Lyme disease (eg, Borrelia burgdorferi, Borrelia garinii, Borrelia afzelii)

**Interpretation:**
- Negative (Lyme CNS AI 0.6 to <1.3): Results indicate lack of intrathecal antibody synthesis to Lyme disease associated Borrelia species. This suggests the absence of neuroinvasive Lyme disease. The initial screen reactive result may be due to anti-Borrelia species antibodies present in the cerebrospinal fluid (CSF) due to increased permeability of the blood-brain barrier or transient introduction during lumbar puncture.
- Equivocal (Lyme CNS AI 1.3 to 1.5): Low level of intrathecal antibody synthesis to Lyme disease associated Borrelia species detected. Results should be correlated with exposure history and clinical presentation to establish a diagnosis of neuroinvasive Lyme disease.
- Positive (Lyme CNS AI >1.5): Results indicate the presence of intrathecal antibody synthesis to Lyme disease associated Borrelia species, suggesting neuroinvasive Lyme disease. Results should be correlated with exposure history and clinical presentation to establish the diagnosis.
- Invalid (Lyme CNS AI <0.6): Result is due to abnormally elevated total IgG levels in CSF. This may be due to passive diffusion through the blood-brain barrier or contamination of the CSF with blood during a traumatic lumbar puncture. Repeat testing may be considered.

**Reference Values:**
Only orderable as part of a profile. For more information see LNBAB / Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid.

0.6-1.2


**LYWB 9535**

**Lyme Disease Antibody, Immunoblot, Serum**

**Clinical Information:** Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema chronicum migrans (ECM), a unique expanding skin lesion with central clearing, which results in a ring-like appearance, is the first stage of the disease. Any of the following clinical manifestations may be present in patients with Lyme disease: arthritis, neurological or cardiac disease, or skin lesions. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall having a tick bite or a rash. The Second National Conference on the Serologic Diagnosis of Lyme Disease (1994) recommended that laboratories use a 2-test approach for the serologic diagnosis of Lyme disease. Accordingly, specimens are first tested by the more sensitive enzyme immunoassay (EIA). An immunoblot assay is used to supplement positive or equivocal Lyme (EIA). An immunoblot identifies the specific proteins to which the patient's antibodies bind. Although there are no proteins that specifically diagnose B burgdorferi infection, the number of proteins recognized in the immunoblot assay is correlated with diagnosis. Culture or polymerase chain reaction (PCR) of skin biopsies obtained near the margins of ECM are frequently positive. In late (chronic) stages of the disease, serology is often positive and the diagnostic method of choice. PCR testing also may be of use in these late stages if performed on synovial fluid or cerebrospinal fluid. Diagnosis of neuroinvasive Lyme disease (ie, neuroborreliosis) can be achieved by
determining the Lyme antibody index value using paired serum and cerebrospinal fluid samples (LNBAB / Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid).

**Useful For:** Aiding in the diagnosis of systemic Lyme disease This test should not be used as a screening assay.

**Interpretation:** IgM: IgM antibodies to Borrelia burgdorferi may be detectable within 1 to 2 weeks following the tick bite; they usually peak during the third to sixth week after disease onset, and then demonstrate a gradual decline over a period of months. IgM antibody may persist for months following completion of treatment. IgM antibody results against B burgdorferi should only be considered during the 30 days following exposure and symptom onset. Negative specimens typically demonstrate antibodies to fewer than 2 of the 3 significant B burgdorferi proteins. Additional specimens should be submitted in 2 to 3 weeks if B burgdorferi exposure has not been ruled out. IgG: IgG antibodies to B burgdorferi can be detected approximately 2 weeks after onset of disease and can remain detectable for months to years following completion of therapy. Normal specimens and false-positive enzyme immunoassay (EIA) specimens generally have antibodies to 4 or fewer proteins. Except for early patients, antibodies from patients with Lyme disease generally bind to 5 or more proteins.

**Reference Values:**
- IgG: Negative
- IgM: Negative

**Reference values apply to all ages**


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**ELYME 65417**

**Lyme Disease European Antibody Screen, Serum**

**Clinical Information:** Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex. Among the genospecies within this complex, B burgdorferi sensu stricto (B burgdorferi) is the primary agent causing LD in North America. While B burgdorferi is also found abroad, Borrelia garinii and Borrelia afzelii are more prevalent in Europe and regions of Asia. These spirochetes are transmitted to humans through the bite of Ixodes species ticks, primarily Ixodes ricinus and, to a lesser extent, Ixodes persulcatus, which are both found throughout Europe, the Baltic regions, and parts of Asia. Therefore, residents of, or travelers to, these areas who are bitten by ticks are at increased risk for LD caused by a European Borrelia species. Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronic arothrophicans (ACA), typically due to infection with B afzelii. Diagnosis of LD is currently based on a 2-tiered serologic testing algorithm to detect antibodies to LD-associated Borrelia species. Importantly, patients may be seronegative until 2 weeks post onset of symptoms. An IgM-class antibody response usually peaks 3 to 6 weeks after infection but may persist for years in some cases. IgG-class antibodies to Borrelia spirochetes are detectable 2 to 3 weeks postinfection and may remain elevated for years after resolution of symptoms. In patients with EM, culture of skin biopsies obtained near the margins of the rash are frequently positive, though this technique is not commonly available. In late (chronic) stages of the disease, serology is often positive and is the diagnostic method of choice. Polymerase chain reaction (PCR) testing may also be of use in these late stages if performed on synovial fluid or tissue. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Also, if provided early in disease, treatment may suppress the immune response to the bacteria leading to negative serologic results. The 2-tiered testing algorithm for LD involves an initial screening assay for detection of total antibodies to LD-causing Borrelia species. For this algorithm, the C6 enzyme-linked immunosorbent assay (ELISA) is used to screen all specimens, and those with positive or equivocal results are reflexed for supplemental testing by immunoblot for detection of IgM and IgG.
antibodies to LD-causing Borrelia species. Importantly, while most screening ELISAs detect antibodies to all major LD-associated Borrelia species, the immunoblots used for supplemental testing in North America are specifically designed to detect antibodies to the B burgdorferi B31 strain. Despite similarity between the genospecies, the North America immunoblots have a reported sensitivity of approximately 50% for LD caused by the European Borrelia species (eg, B afzelii and B garinii). In order to improve upon the ability to detect antibodies to the European Borrelia species, immunoblot tests designed to detect IgM- and IgG-class antibodies B garinii, B afzelii and B burgdorferi are used for supplemental testing of all specimens with positive or equivocal results by the LD screening ELISA.

**Useful For:** Aiding in the diagnosis of Lyme disease caused by infection with Borrelia species endemic to Europe and Asia, including Borrelia garinii and Borrelia afzelii This test should not be used to screen the general population. It is only intended for use in patients with recent travel to and exposure to ticks in Europe or regions of Asia who are suspected to have Lyme disease caused by Borrelia species endemic to Europe/Asia.

**Interpretation:** Negative result: No antibodies to Lyme disease Borrelia species (eg Borrelia afzelii, Borrelia burgdorferi, Borrelia garinii) detected. Repeat testing on a new specimen collected in 2 to 3 weeks should be considered if acute Lyme disease due to one of these Borrelia species is suspected. Equivocal result: Not diagnostic. Supplemental immunoblot testing has been ordered by reflex. Positive result: Not diagnostic. Supplemental immunoblot testing has been ordered by reflex.

**Reference Values:**

Negative

**Clinical References:**

**ELYMI** 65418

**Lyme Disease European Immunoblot, Serum**

**Clinical Information:** Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex. Among the genospecies within this complex, B burgdorferi sensu stricto (B burgdorferi) is the primary agent causing LD in North America. While B burgdorferi is also found abroad, Borrelia garinii and Borrelia afzelii are more prevalent in Europe and regions of Asia. These spirochetes are transmitted to humans through the bite of Ixodes species ticks, primarily Ixodes ricinus and to a lesser extent Ixodes persulcatus, which are both found throughout Europe, the Baltic regions, and parts of Asia. Therefore, residents of or travelers to these areas who are bitten by ticks are at increased risk for LD caused by a European Borrelia species. Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique, expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans (ACA), typically due to infection with B afzelii. Diagnosis of LD is currently based on a 2-tiered serologic testing algorithm to detect antibodies to LD-associated Borrelia species. Importantly, patients may be seronegative until 2 weeks post onset of symptoms. An IgM-class antibody response usually peaks 3 to 6 weeks after infection but may persist for years in some cases. IgG-class antibodies to Borrelia spirochetes are detectable 2 to 3 weeks postinfection and may remain elevated for years after resolution of symptoms. In patients with EM, culture of skin biopsies obtained near the margins of the rash, are frequently positive, though this technique is not commonly available. In late (chronic) stages of the disease, serology is often positive and is the diagnostic method of choice. Polymerase chain reaction (PCR) testing may also be of use in these late stages if performed on synovial fluid or tissue. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Also, if provided early in disease, treatment may suppress the immune response to the bacteria leading to negative serologic results. The 2-tiered testing
Algorithm for LD involves an initial screening assay for detection of total antibodies to LD-causing Borrelia species. For this algorithm, the C6 enzyme-linked immunosorbent assay (ELISA) is used to screen all specimens and those with positive or equivocal results are reflexed for supplemental testing by immunoblot for detection of IgM and IgG antibodies to LD-causing Borrelia species. Importantly, while most screening ELISAs detect antibodies to all major LD-associated Borrelia species, the immunoblots used for supplemental testing in North America are specifically designed to detect antibodies to the B. burgdorferi B31 strain. Despite similarity between the genospecies, the North America immunoblot tests have a reported sensitivity of approximately 50% for LD caused by the European Borrelia species (eg, B. afzelii and B. garinii). In order to improve upon our ability to detect antibodies to the European Borrelia species, immunoblot tests designed to detect IgM and/or IgG-class antibodies B. garinii, B. afzelii, and B. burgdorferi are used for supplemental testing of all specimens with positive or equivocal results by the LD screening ELISA.

**Useful For:** Aiding in the diagnosis of Lyme disease caused by infection with Borrelia species endemic to Europe and Asia, including B. garinii or B. afzelii; This test is only intended for use in patients with recent travel to and exposure to ticks in Europe or regions of Asia who are suspected to have Lyme disease caused by Borrelia species endemic to Europe/Asia; This test should not be used to screen the general population.

**Interpretation:** Immunoglobulin M: The interpretation of IgM immunoblots for Lyme disease caused by Borrelia species endemic to Europe differs from the interpretative criteria for IgM immunoblots used for evaluation of Lyme disease caused by Borrelia burgdorferi in North America. The European Lyme disease IgM immunoblot interpretive criteria is as follows: -Positive: The presence of a band at 1 or more of the following 5 proteins - p39, OspC, Osp17 (DbpA), VlsE, and/or p41 (high intensity) -Interpretation: Specific antibodies against Lyme disease associated Borrelia species detected suggesting recent infection. -Negative: No distinct bands -Interpretation: No specific antibodies against Lyme disease associated Borrelia species were detected. If infection remains suspected, repeat testing on a new specimen collected in 2 to 3 weeks is suggested. IgM-class antibodies to Borrelia species that cause Lyme disease, including Borrelia afzelii and Borrelia garinii, may be detectable as early as 1 to 2 weeks following a tick bite, however, they typically peak during the third to sixth week postinfection. IgM-class antibodies to these agents may persist for months following disease resolution and antimicrobial treatment. Results of the IgM immunoblot should only be interpreted and considered during the first 4 to 6 weeks after disease onset. Patients tested soon after disease onset may be negative for IgM-class antibodies to Lyme disease-associated Borrelia species. Repeat testing should be performed in 2 to 3 weeks if infection with a European species of Borrelia continues to be suspected. Immunoglobulin G: The interpretation of IgG immunoblots for Lyme disease caused by Borrelia species endemic to Europe differs from the interpretative criteria for IgG immunoblots used to for evaluation of Lyme disease caused by B burgdorferi in North America. The European Lyme disease IgG immunoblot is interpreted as follows: -Positive: The presence of a band at 2 or more of the following 10 proteins: p38, p58, p43, p39, p30, OspC, p21, Osp17 (DbpA), p14, VlsE -Interpretation: Specific antibodies against Lyme disease associated Borrelia species were detected, suggesting infection at some point in the recent or remote past. Clinical correlation required. -Equivocal: One distinct band at the VlsE protein only -Interpretation: Specific antibodies to the VlsE protein of Lyme disease associated Borrelia species were detected, suggesting possible infection. Repeat testing on a new specimen collected in 2 to 3 weeks is recommended to confirm infection. -Negative: One or no distinct bands (except VlsE) -Interpretation: No specific antibodies against Lyme disease-associated Borrelia species were detected. If infection remains suspected, repeat testing on a new specimen collected in 2 to 3 weeks is suggested. IgG-class antibodies to Lyme disease causing Borrelia species may remain detectable for months to years following resolution of disease and/or antimicrobial treatment.

**Reference Values:**
Only orderable as a reflex. For more information see ELYME / Lyme Disease European Antibody Screen, Serum.

IgG: Negative
IgM: Negative
Reference values apply to all ages.

**Clinical References:** 1. Branda JA, Strle F, Strle K, Sikand N, Ferraro MJ, Steere AC; Performance
Lyme Disease Serology, Serum

**Clinical Information:** Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex, which includes B burgdorferi sensu stricto (herein referred to as B burgdorferi), Borrelia afzelii, and Borrelia garinii. Among these species, B burgdorferi is the most frequent cause of LD in North America. These tick-borne spirochetes are transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes scapularis (Northeastern and upper Midwestern US) and Ixodes pacificus (West Coast US). Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans (ACA), typically due to infection with B afzelii. Diagnosis of LD is currently based on a 2-tiered serologic testing algorithm, as recommended by the Centers for Disease Control and Prevention (CDC), and involves an initial screening assay for detection of antibodies to LD-causing Borrelia species. Samples that are screen positive or equivocal are subsequently reflexed for supplemental assessment using a B burgdorferi immunoblot for detection of IgM- and IgG-class antibodies to specific B burgdorferi antigens. Importantly, while serologic assessment for LD may be negative in the early weeks following infection, over 90% of patients with later stages of infection are seropositive by serology, which remains the diagnostic method of choice for this disease.

**Useful For:** Diagnosis of Lyme disease This test should not be used as a screening procedure for the general population. This test should not be used for treatment monitoring.

**Interpretation:** Negative: No evidence of antibodies to Borrelia burgdorferi detected. False-negative results may occur in recently infected patients (< or =2 weeks) due to low or undetectable antibody levels to B burgdorferi. If recent exposure is suspected, a second specimen should be collected and tested in 2 to 4 weeks. Equivocal: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex. Positive: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex.

**Reference Values:**
Negative
Reference values apply to all ages.


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Lyme Disease, Molecular Detection, PCR, Blood

**Clinical Information:** Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (BbSL) complex.(1) Nearly all human infections are caused by 3 BbSL species; B burgdorferi sensu stricto (hereafter referred to as B...
burgdorferi) is the primary cause of Lyme disease in North America, while B. afzelii and B. garinii are the primary causes of Lyme disease in Europe. In 2012, B. mayonii was identified as a less common cause of Lyme disease in the upper Midwestern United States.(2,3) This organism has only been detected in patients with exposure to ticks in Minnesota and Wisconsin and has not been detected in over 10,000 specimens from patients in other states including regions of the northeast where Lyme disease is endemic. Lyme disease is the most commonly reported tick-borne infection in Europe and North America, causing an estimated 300,000 cases in the United States each year, and 85,000 cases in Europe.(4,5) The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B. burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. Erythema migrans has also been seen in patients with B. mayonii infection, but diffuse rashes are more commonly reported.(2) The chronic skin condition, acrodermatitis chronica atrophicans, is also associated with B. afzelii infection.

The presence of EM in the appropriate clinical setting is considered diagnostic for Lyme disease and no confirmatory laboratory testing is needed. In the absence of a characteristic EM lesion, serologic testing is the diagnostic method of choice for Lyme disease.(6) However, serology may not be positive until 1 to 2 weeks after onset of symptoms, and may show decreased sensitivity for detection of infection with B. mayonii. Therefore, detection of Bsbl DNA using PCR may be a useful adjunct to serologic testing for detection of acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of Lyme-associated rashes, and can also be used to detect Borrelia DNA from synovial fluid and synovium biopsies. Less commonly, Borrelia DNA can be detected in cerebrospinal fluid and blood.(7) In general, blood is not the preferred source for detection of Bsbl DNA by PCR, although it may have increased utility for detection of B. mayonii, due to the higher levels of observed peripheral spirochetemia with this organism.(2) Lyme PCR should always be performed in conjunction with FDA-approved serologic tests, and results should be correlated with serologic and epidemiologic data and clinical presentation of the patient.(8) The Mayo Clinic Lyme PCR test detects and differentiates the main causes of Lyme disease in North America (B. burgdorferi and B. mayonii) and Europe (B. afzelii and B. garinii).(2,7)

**Useful For:** Supporting the diagnosis of Lyme disease in conjunction with serologic testing

**Interpretation:** A positive result indicates the presence of DNA from Borrelia burgdorferi, B. mayonii, B. afzelii, or B. garinii, the main agents of Lyme disease. A negative result indicates the absence of detectable target DNA in the specimen. Due to the diagnostic sensitivity limitations of the PCR assay, a negative result does not preclude the presence of the organism or active Lyme disease.

**Reference Values:**

- Negative

**Clinical References:**

Lyme Disease, Molecular Detection, PCR, Varies

Clinical Information: Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex.(1) Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while B afzelii and B garinii are the primary causes of Lyme disease in Europe. In 2012, B mayonii has been identified as a less common cause of Lyme disease in the upper Midwestern United States.(2,3) This organism has only been detected in patients with exposure to ticks in Minnesota and Wisconsin and has not been detected in over 10,000 specimens from patients in other states including regions of northeast where Lyme disease is endemic. Lyme disease is the most commonly reported tick-borne infection in Europe and North America, causing an estimated 300,000 cases in the United States each year, and 85,000 cases in Europe.(4,5) The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. Erythema migrans has also been seen in patients with B mayonii infection, but diffuse rashes are more commonly reported.(2) The chronic skin condition, acrodermatitis chronica atrophicans, is also associated with B afzelii infection. The presence of EM in the appropriate clinical setting is considered diagnostic for Lyme disease and no confirmatory laboratory testing is needed. In the absence of a characteristic EM lesion, serologic testing is the diagnostic method of choice for Lyme disease.(6) However, serology may not be positive until 1 to 2 weeks after onset of symptoms, and may show decreased sensitivity for detection of infection with B mayonii. Therefore, detection of Bbsl DNA using PCR may be a useful adjunct to serologic testing for detection of acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of Lyme-associated rashes and also be used to detect Borrelia DNA from synovial fluid and synovium biopsies. Less commonly, Borrelia DNA can be detected in cerebrospinal fluid.(7) Lyme PCR should always be performed in conjunction with FDA-approved serologic tests, and the results should be correlated with serologic and epidemiologic data and clinical presentation of the patient.(8) The Mayo Clinic Lyme PCR test detects and differentiates the main causes of Lyme disease in North America (B burgdorferi and B mayonii) and Europe (B afzelii and B garinii).(2,7)

Useful For: Supporting the diagnosis of Lyme disease in conjunction with serologic testing Specific indications including testing skin biopsies when a rash lesion is not characteristic of erythema migrans, and testing synovial fluid or synovium to support the diagnosis of Lyme arthritis

Interpretation: A positive result indicates the presence of DNA from Borrelia burgdorferi, B mayonii, B afzelii, or B garinii, the main agents of Lyme disease. A negative result indicates the absence of detectable target DNA in the specimen. Due to the clinical sensitivity limitations of the PCR assay, a negative result does not preclude the presence of the organism or active Lyme disease.

Reference Values:
Negative

T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, (NK)-cell counts, on the other hand, is constant throughout the day. Circadian variations in circulating B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The absolute counts visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be fluorescent signal is then measured by flow cytometry.(9) Specific proliferating cell populations can be catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, alkyne-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(8) In the assay, an direct detection of nucleotide incorporation. The Click-iT-EdU assay has been shown to be an acceptable Invitrogen Click-iT-EdU assay, the click chemistry has been adapted to measure cell proliferation through that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. In the Clinical Information: T-cell stimulation in vitro is used extensively in the diagnostic immunology arena for facilitating T-cell proliferation and evaluation of T-cell function in a variety of clinical contexts.(1,2) The widely used method for assessing lymphocyte proliferation has been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1) the technique is cumbersome due to the use of radioactivity; 2) it does not allow discrimination of responding cell populations in response to stimulation; and 3) it does not provide any information on the contribution of apoptosis or cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation, decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and underrepresentation of T cells in the peripheral blood mononuclear cell pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or sample. While mitogens such as phytohemagglutinin (PHA) activate T cells by binding to cell membrane glycoproteins, including the T-cell receptor (TCR)-CD3 complex, there are a number of mitogenic or comitogenic antibodies, including those directed against the CD3 coreceptor that can stimulate T-cell proliferation. Typically, anti-CD3 antibodies provide an initial activation signal, but do not induce significant proliferation, and the addition of a costimulatory antibody (anti-CD28) provides the stimulus for robust proliferation.(3) An exogenous T-cell growth factor, such as interleukin-2 (IL-2), may also be used as an alternate to anti-CD28 costimulation, and in patients with suspected IL-2 receptor-associated signaling defects, it may be more helpful than the use of anti-CD28. IL-2, an autocrine cytokine, has been demonstrated to be critical in T-cell proliferation.(4,5) The interaction of IL-2 with the IL-2 receptor (IL-2R) plays a central role in regulation of T-cell proliferation.(4) Triggering of the TCR leads to synthesis of IL-2 in certain T-cell subsets and induction of high-affinity IL-2Rs in antigen- or mitogen-activated T cells, and the binding of IL-2 to IL-2R ultimately leads to T-cell proliferation. The use of exogenous IL-2 in association with anti-CD3 allows discrimination of whether T cells, which cannot proliferate to other mitogenic signals, can respond to a potent growth factor such as IL-2. Stimulation of T cells with soluble antibodies to anti-CD3 (and the associated TCR complex) causes mobilization of cytoplasmic calcium and translocation of protein kinase C from the cytoplasm to the cell membrane. This stimulation also causes induction of phosphatidylinositol metabolism and subsequent IL-2 production for proliferation.(6) T-cell activation induced by anti-CD3 antibody requires prolonged stimulation of protein kinase C, which apparently can be achieved by the concomitant use of the anti-CD28 antibody for costimulation without addition of other mitogenic stimuli, such as phorbol myristate acetate (PMA).(7) This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. In the Invitrogen Click-iT-EdU assay, the click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. The Click-iT-EdU assay has been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(8) In the assay, an alkyne-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry.(9) Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK)-cell counts, on the other hand, is constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact,
cortisol and catecholamine concentrations control distribution and, therefore, the numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing, and consistency in timing, of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** A second-level test after lymphocyte proliferation to mitogens (specifically phytohemagglutinin) has been assessed. The anti-CD3 proliferation panel is not a first-level test for assessing lymphocyte (T-cell) function Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency [SCID], etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation Evaluation of T-cell function in patients receiving immunosuppressive or immunomodulatory therapy Evaluation of T-cell function in the context of identifying neutralizing antibodies in patients receiving therapeutic anti-CD3 antibody immunosuppression for solid organ transplantation or autoimmune diseases, such as type 1 diabetes

**Interpretation:** Abnormal test results to anti-CD3/aCD28/interleukin-2 (IL-2) stimulation are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with underrepresentation of T cells within the peripheral blood mononuclear cells (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. The evaluation of T-cell proliferation to anti-CD3/IL-2 is likely to be helpful in assessing T-cell function in patients with refractory responses to other mitogenic and antigenic stimuli, specifically in the context of IL-2-receptor signaling defects, enabling greater mechanistic insight into the origins of T-cell dysfunction. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to any mitogenic stimulus, including anti-CD3/anti-CD28, can be regarded as a more specific but less sensitive test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of identification of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age, and a continuing decline through adolescence to half the neonatal response.(10) In our evaluation of 43 pediatric samples (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for the mitogens, pokeweed mitogen (PWM) and phytohemagglutinin (PHA), respectively. Comparisons between pediatric and adult data have not been performed for anti-CD3/aCD28 due to unavailability of prospective blood samples from healthy or patient pediatric donors for purposes of analytical validation. It should be noted that without obtaining formal pediatric reference values it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens (including anti-CD3 stimulation) and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed greater than 24 and less than 48 hours post blood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

**Reference Values:**

- Viability of lymphocytes at day 0: > or =75.0%
- Maximum proliferation of anti-CD3 as % CD45: > or =19.4%
- Maximum proliferation of anti-CD3 as % CD3: > or =20.3%
Maximum proliferation of anti-CD3 + anti-CD28 as % CD45: > or =37.5%
Maximum proliferation of anti-CD3 + anti-CD28 as % CD3: > or =44.6%
Maximum proliferation of anti-CD3 + IL-2 as % CD45: > or =41.7%
Maximum proliferation of anti-CD3 + IL-2 as % CD3: > or =46.2%


**Clinical Information:** Determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with recall antigens, including Candida albicans (CA) and tetanus toxoid (TT), has been part of the diagnostic immunology repertoire for many years.(1,2) The widely used method for assessing lymphocyte proliferation to antigens has hitherto been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity. 2. It does not allow discrimination of responding cell populations in response to stimulation. 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under representation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or sample. Antigens, like CA and TT, have been widely used to measure antigen-specific recall (anamnestic) T-cell responses when assessing cellular immunity. In fact, it may be more revealing about cellular immune compromise than assessing the response of lymphocytes to mitogens because the latter can induce T-cell proliferative responses even if those T cells are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to antigens are considered a diagnostically more sensitive, but less specific, test of aberrant T-cell function.(2) Antigens used in recall assays measure the ability of T cells bearing specific T-cell receptors (TCR) to respond to such antigens when processed and presented by antigen-presenting cells. The antigens used for assessment of the cellular immune response are selected to represent antigens, seen by a majority of the population, either through natural exposure (CA) or as a result of vaccination (TT). This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of Click chemistry. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The Click-iT-EdU assay has shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(3) The degree of impairment of antigen-specific T-cell responses can vary depending on the nature of the cellular immune compromise. For example, some, but not all, patients
with partial DiGeorge syndrome, a primary cellular immunodeficiency, have been reported to have either
decreased or absent T-cell responses to CA and TT.(4) Similarly, relative immune compromise, especially
to TT, has been reported in children with vitamin A deficiency, but the measurements have been largely
of the humoral immune response. Since this requires participation of the cellular immune compartment, it
can be postulated that there could be a potential impairment of antigen-specific T-cell responses as
well.(5)

**Useful For:** Assessing T-cell function in patients on immunosuppressive therapy, including
solid-organ transplant patients Evaluating patients suspected of having impairment in cellular immunity
Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge
syndrome, T-negative severe combined immunodeficiency; SCID, etc) or combined T- and B-cell
immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia,
common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation
of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic
Evaluation of recovery of T-cell function and competence following bone marrow transplantation or
hematopoietic stem cell transplantation This test is not intended for assessment of maternal engraftment.

**Interpretation:** Abnormal test results to antigen stimulation are indicative of impaired T-cell
function, if T-cell counts are normal or only modestly decreased. If there is profound T-cell
lymphopenia, there could be a dilution effect with underrepresentation of T cells within the peripheral
blood mononuclear cell (PBMC) population that could result in lower T-cell proliferative responses.
However, this is not a significant concern in the flow cytometry assay, since acquisition of additional
cellular events during analysis can compensate for artificial reduction in proliferation due to lower
T-cell counts. In the case of antigen-specific T-cell responses to tetanus toxoid (TT), there can be absent
responses due to natural waning of cellular immunity, if the interval between vaccinations has exceeded
the recommended period, especially in adults. In such circumstances, it would be appropriate to
measure TT-specific T-cell responses 4 to 6 weeks after a booster vaccination. There is no absolute
correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether
primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient,
for an effective immune response. Therefore, the proliferative response to antigens can be regarded as a
more sensitive, but less specific, test for the diagnosis of infection susceptibility. There is no single
laboratory test that can identify or define impaired cellular immunity, with the exception of an
opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults.
Since this test is used for screening and evaluating cellular immune dysfunction in infants and children,
it is reasonable to question the comparability of proliferative responses between healthy infants,
children, and adults. It is reasonable to expect robust T-cell-specific responses to TT in children without
 cellular immune compromise, as a result of repeated childhood vaccinations. The response to Candida
albicans can be more variable depending on the extent of exposure and age of exposure. A comment
will be provided in the report documenting the comparison of pediatric results with an adult reference
range and correlation with clinical context for appropriate interpretation. Without obtaining formal
pediatric reference values, there remains a possibility that the response in infants and children can be
underestimated. However, the practical challenges of generating a pediatric range for this assay
necessitate comparison of pediatric data with adult reference values or controls.

**Reference Values:**
Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of Candida albicans as % CD45: > or =5.7%
Maximum proliferation of Candida albicans as % CD3: > or =3.0%
Maximum proliferation of tetanus toxoid as % CD45: > or =5.2%
Maximum proliferation of tetanus toxoid as % CD3: > or =3.3%

**Clinical References:**
1. Dupont B, Good RA: Lymphocyte transformation in vitro in patients with
immunodeficiency diseases: use in diagnosis, histocompatibility testing and monitoring treatment. Birth
HH, Bonilla FA: Analysis of in vitro lymphocyte proliferation as a screening tool for cellular
Gruenebaum E: EdU-Click iT flow cytometry assay as an alternative to 3H-thymidine for measuring
LPMGF Lympocyte Proliferation to Mitogens, Blood

Clinical Information: The method of determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with mitogenic plant lectins (mitogens) such as phytohemagglutinin (PHA) and pokeweed mitogen (PWM) has been part of the diagnostic immunology repertoire for many years. The widely used method for assessing lymphocyte proliferation has hitherto been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity. 2. It does not allow discrimination of responding cell populations in response to stimulation. 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under-representation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. Mitogens are very potent stimulators of T-cell activation and proliferation independent of their antigenic specificity. It has been suggested that mitogens can induce T-cell proliferative responses even if they are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to mitogens are considered a diagnostically less sensitive, but more specific, test of aberrant T-cell function. Lectin mitogens have been shown to bind the T-cell receptor, which is glycosylated through its carbohydrate moiety, thereby activating quiescent T cells. Mitogenic stimulation has been shown to increase intracellular calcium (Ca^{2+}) in T cells, which is essential for T-cell proliferation. While PHA is a strong T-cell mitogen, PWM is a weak T-cell mitogen, but it induces B-cell activation and proliferation as well. This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of Click chemistry. In the Invitrogen Click-iT-EdU assay, the Click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. In the assay, an alkyne-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry. Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The Click-iT-EdU assay has shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK)-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts negatively correlate with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ transplant patients. Evaluating patients suspected of having impairment in cellular immunity.
T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency: SCID, etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation

**Interpretation:** Abnormal test results to mitogen stimulation are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, there could be a dilution effect with under-representation of T cells within the peripheral blood mononuclear cell (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to mitogens can be regarded as more specific, but less sensitive, test for the diagnosis of infection susceptibility. There is no single laboratory test that can identify or define impaired cellular immunity, with the exception of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age and a continuing decline through adolescence to half the neonatal response. In an in-house evaluation of 43 pediatric specimens (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for pokeweed (PWM) and phytohemagglutinin (PHA), respectively. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. Without obtaining formal pediatric reference values, there remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed between 24- and 48-hours post-blood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context

**Reference Values:**

Viability of lymphocytes at day 0: > or =75.0%

- Maximum proliferation of phytohemagglutinin as % CD45: > or =49.9%
- Maximum proliferation of phytohemagglutinin as % CD3: > or =58.5%
- Maximum proliferation of pokeweed mitogen as % CD45: > or =4.5%
- Maximum proliferation of pokeweed mitogen as % CD3: > or =3.5%
- Maximum proliferation of pokeweed mitogen as % CD19: > or =3.9%

**Clinical References:**

**LEF1**

**Lymphoid Enhancer-Binding Factor 1 (LEF1) Immunostain, Technical Component Only**

**Clinical Information:** Lymphoid enhancer-binding factor 1 (LEF1) is a transcription factor that participates in the activation of genes within the Wnt signaling pathway. LEF1 is expressed by inactive T-cells and a subset of B-cells.

**Useful For:** Differentiating cancers of B-cell origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**LPLFX**

**Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia (LPL/WM), MYD88 L265P with Reflex to CXCR4, Varies**

**Clinical Information:** The MYD88 L265P abnormality is highly associated (>90%) with the pathologic diagnosis of lymphoplasmacytic lymphoma and the clinical syndrome of Waldenstrom macroglobulinemia (LPL/WM), particularly in the setting of an elevated IgM serum monoclonal paraprotein. CXCR4 variants are identified in approximately 30% to 40% of LPL/WM patients and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 variants in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival and therapeutic response to ibrutinib: A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift variants) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients. A MYD88-L265P/CXCR4-WT (wild type) molecular signature is associated with intermediated bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients. A MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 variant.

**Useful For:** Establishing the diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) Helping distinguish LPL/WM low-grade B-cell lymphoma from other subtypes Aiding in the prognostication and clinical management of LPL/WM

**Interpretation:** Variant present or not detected; an interpretive report will be issued.
Reference Values:
MYD88 L265P: Variant present or absent based on expected variant PCR product size for the MYD88 gene (NCBI accession NM_002468.4).

CXCR4: Variants present or absent in the test region c. 898-1059 (amino acids 300-353) of the CXCR4 gene (NCBI NM_003467.2, GRCh37).

Clinical References:

Lynch Syndrome Panel, Varies

Clinical Information: While the risk for colorectal cancer in the general population is 6%, rarely colon cancer is attributable to hereditary factors associated with a single abnormal gene that predisposes individuals to increased risks for cancer in a family. Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3' end of the EPCAM gene, which lead to inactivation of the MSH2 promotor, have also been associated with Lynch syndrome. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated with MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with Lynch syndrome.

Useful For: Establishing a diagnosis of Lynch syndrome Identification of familial MLH1, MSH2, MSH6, PMS2, or EPCAM variants to allow for predictive testing in family members
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**LPCBS 61766**

**Lysophosphatidylcholines by LC MS/MS, Blood Spot**

**Clinical Information:** This assay measures C20, C22, C24, and C26 lysophosphatidylcholine (LPC) species in dried blood spots by liquid chromatography-tandem mass spectrometry. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects such as Zellweger spectrum syndrome are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants. X-linked adrenoleukodystrophy (X-ALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. At least 50% of all females who are heterozygotes for X-ALD are symptomatic. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation. Elevations of C24 lysophosphatidylcholine (LPC) and C26 LPC may be indicative of X-ALD. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Therefore, measurement of LPCs is a useful second-tier test for newborn screening for X-ALD. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger...
syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. Although ZSS disorders are not a primary disease target for testing, this test will detect infants with these disorders.

**Useful For:** Second-tier newborn screen for X-linked adrenoleukodystrophy (X-ALD)

**Interpretation:** An interpretive report will be provided. In females: Elevations of C24 LPC or C26 LPC may be indicative of heterozygosity for X-linked adrenoleukodystrophy (X-ALD), or other forms of peroxisomal disorders. In males: Elevations of C24 LPC or C26 LPC may be indicative of X-ALD or other forms of peroxisomal disorders. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

**Reference Values:**

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<thead>
<tr>
<th>Analyte</th>
<th>Normal Range (mcg/mL)</th>
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<tr>
<td>C20 Lysophosphatidylcholine</td>
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<tr>
<td>C22 Lysophosphatidylcholine</td>
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</tr>
<tr>
<td>C24 Lysophosphatidylcholine</td>
<td>&lt; or =0.25</td>
</tr>
<tr>
<td>C26 Lysophosphatidylcholine</td>
<td>&lt; or =0.20</td>
</tr>
</tbody>
</table>

**Clinical References:**

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**Lysosomal Acid Lipase, Blood**

**Clinical Information:** Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by variant in the LIPA gene. WD, the early-onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, hepatosplenomegaly, and liver failure. Enlarged adrenal glands with calcification, a classic finding in WD, can lead to adrenal cortical insufficiency. Unless successfully treated, survival is rare beyond infancy. CESD, the late-onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, serum lipid abnormalities, and elevated liver enzymes. In childhood, patients can also present with failure to thrive and delayed milestones. Common features include premature atherosclerosis leading to coronary artery disease and strokes, liver disease of varying severity, and organomegaly. Lipid deposition in the intestinal tract can lead to diarrhea and weight loss. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Enzyme replacement therapy (sebelipase alfa) was recently approved for both WD and CESD and is now clinically available.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency using blood specimens This test is not useful to determine carrier status for cholesteryl ester storage disease or Wolman disease.
**Interpretation:** Enzyme activity below 1.5 nmol/hour/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency: Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/hour/mL) are not consistent with lysosomal acid lipase deficiency.

**Reference Values:**
> or =21.0 nmol/hour/mL

**Clinical References:**

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**LALBS 62955**

**Lysosomal Acid Lipase, Blood Spot**

**Clinical Information:** Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by variant in the LIPA gene. WD, the early-onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, hepatosplenomegaly, and liver failure. Enlarged adrenal glands with calcification, a classic finding in WD, can lead to adrenal cortical insufficiency. Unless successfully treated, survival is rare beyond infancy. CESD, the late-onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, serum lipid abnormalities, and elevated liver enzymes. In childhood, patients can also present with failure to thrive and delayed milestones. Common features include premature atherosclerosis leading to coronary artery disease and strokes, liver disease of varying severity, and organomegaly. Lipid deposition in the intestinal tract can lead to diarrhea and weight loss. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Enzyme replacement therapy (sebelipase alfa) was recently approved for both WD and CESD, and is now clinically available.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency using blood spot specimens. This test is not useful to determine carrier status for cholesteryl ester storage disease or Wolman disease.

**Interpretation:** Enzyme activity below 1.5 nmol/hour/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency: Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/hour/mL) are not consistent with lysosomal acid lipase deficiency.

**Reference Values:**
> or =21.0 nmol/hour/mL

**Clinical References:**

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**LDALD 64907**

**Lysosomal and Peroxisomal Disorders Newborn Screen, Blood Spot**

**Clinical Information:** Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by variant in the LIPA gene. WD, the early-onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, hepatosplenomegaly, and liver failure. Enlarged adrenal glands with calcification, a classic finding in WD, can lead to adrenal cortical insufficiency. Unless successfully treated, survival is rare beyond infancy. CESD, the late-onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, serum lipid abnormalities, and elevated liver enzymes. In childhood, patients can also present with failure to thrive and delayed milestones. Common features include premature atherosclerosis leading to coronary artery disease and strokes, liver disease of varying severity, and organomegaly. Lipid deposition in the intestinal tract can lead to diarrhea and weight loss. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Enzyme replacement therapy (sebelipase alfa) was recently approved for both WD and CESD, and is now clinically available.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency using blood spot specimens. This test is not useful to determine carrier status for cholesteryl ester storage disease or Wolman disease.

**Interpretation:** Enzyme activity below 1.5 nmol/hour/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency: Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/hour/mL) are not consistent with lysosomal acid lipase deficiency.

**Reference Values:**
> or =21.0 nmol/hour/mL

**Clinical References:**
**Clinical Information:** Lysosomes are intracellular organelles that contain hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucosylsphingosine (glucosylsphingosine). Gaucher disease is caused by mutations in the GBA gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to an asymptomatic type. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2. Niemann-Pick types A and B are caused by a deficiency of sphingomyelinase due to mutations in the SMPD1 gene. The result is extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of type A versus type B is based on the age of onset as well as the severity of symptoms. Niemann-Pick type A disease is more severe and characterized by early onset with feeding problems, dystrophy, persistent jaundice, cherry red maculae, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of the 2 types is estimated to be 1 in 250,000. Treatment is supportive, although there are clinical trials in place. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. The clinical presentation of Pompe disease ranges from a rapidly progressive infantile variant, which is uniformly lethal if untreated, to a more slowly progressive late-onset variant. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Enzyme replacement therapy is available for all variants and should be started as soon as possible for patients with the infantile variant and at the first signs of muscle weakness in the later onset variants. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by mutations in the GALK gene resulting in a deficiency of galactocerebrosidase (GAL, galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Patients with this early infantile onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Molecular genetic analysis of the GALK gene may provide information on expected age of first symptoms. Psychosine has been shown to be elevated in patients with clinical signs and symptoms of disease and therefore, may be a useful biomarker for the presence of disease or disease progression. The only available therapy is hematopoietic stem cell transplantation that is best performed prior to the onset of clinical symptoms. Early infantile Krabbe disease must, therefore, be considered a critical, time-sensitive newborn screening condition. Fabry disease, caused by mutations in the GLA gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and
corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with more than 1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Pseudodeficiency alleles may also be detected by newborn screening. Treatment with enzyme replacement therapy (ERT) is available for both males and females with Fabry disease. Mucopolysaccharidosis I (MPS-I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Reduced IDUA activity results in accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosomes. The clinical presentation and severity of symptoms of MPS I are variable, ranging from severe disease to attenuated variants (historically known as Hurler-Scheie disease and Scheie disease) that generally present with a later onset and a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. MPS-I is caused by mutations in the IDUA gene and has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomes are organelles present in all human cells except mature erythrocytes. They perform essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects such as Zellweger spectrum syndrome are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants. X-linked adrenoleukodystrophy (XALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. At least 50% of all females who are heterozygotes for XALD are symptomatic. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. Although ZSS disorders are not a primary disease target for testing, this test will detect infants with these disorders.

**Useful For:** First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, mucopolysaccharidosis I (MPS-I), Niemann-Pick types A and B, and Pompe (glycogen storage disorder type II) First-tier newborn screen for the peroxisomal disorder: X-linked adrenoleukodystrophy; may also detect Zellweger spectrum disorders This test is supplemental and not intended to replace state-mandated newborn screening. Test is not intended for metabolic screening of symptomatic patients.

**Interpretation:** An interpretive report will be provided. The quantitative measurements of informative metabolites and related ratios and their bioinformatic evaluation using the Collaborative Laboratory Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn
screen specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic’s Division of Laboratory Genetics and Genomics. The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all of the listed groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn’s results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

**Reference Values:**
Not applicable

**Clinical References:**

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**Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot**

**Clinical Information:** Lysosomes are intracellular organelles that contain hydrolytic enzymes to degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases where macromolecules accumulate due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. Accumulation of these macromolecules in the lysosomes leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of acid beta-glucosidase (glucocerebrosidase: GBA) resulting in increased storage of glucocerebroside (D-glucosylceramide).

The deposition of glucocerebroside in macrophages of the reticuloendothelial system (Gaucher cells) causes organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease: 
- Type I: adult/chronic
- Type II: acute neuropathic/infantile
- Type III: subacute neuropathic/juvenile

Type I, the most frequent form of the disease, is characterized by organomegaly, thrombocytopenia, and bone pain, and is frequent among the Ashkenazim. Hepatosplenomegaly is usually present in all 3 types. Involvement of the central nervous system (CNS) is limited to the infantile type (type II). Enzyme replacement therapy and/or substrate reduction therapy are available for patients with Gaucher disease type I. Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described
with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Sphingomyelinase is encoded by the SMPD1 gene. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, ultimately, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms are characterized by later onset and longer survival with primary symptoms that include muscle weakness and respiratory insufficiency, though rarely, clinically significant cardiomyopathy can be seen. Since Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, when presenting as juvenile and adult-onset forms, is often diagnosed late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment with enzyme replacement therapy is available and improves prognosis, making early diagnosis of Pompe disease desirable. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC; galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. A subset of individuals has later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. They can present anywhere from age 6 months to the seventh decade of life, and based on newborn screening experience in New York, appear to be more common than the earlier onset variants. The clinical course of Krabbe disease can be variable, even within the same family. Of note, Krabbe disease variants, including pseudodeficiency, are not distinguishable by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, is a treatment option with potential benefit. Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occurs in middle age. Males with residual a-Gal A activity greater than1% may present with one of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with end stage renal disease (ESRD) but without the pain or skin lesions, a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD, and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Enzyme replacement therapy is a treatment option for Fabry disease. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisomes are organelles present in all human cells.
except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisome biogenesis defects such as Zellweger spectrum disorders are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to milder, later onset variants. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, and hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. X-linked adrenoleukodystrophy (XALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxosomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes are symptomatic and develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of a lysosomal storage disorder, specifically Gaucher, Niemann-Pick type A or type B, Pompe, Krabbe, Fabry disease, or mucopolysaccharidosis I; or a peroxisomal disorder, either X-linked adrenoleukodystrophy or Zellweger syndrome spectrum

**Interpretation:** An interpretive report will be provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Clinic Laboratories or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

**Reference Values:**

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Lysosomal Storage Disease Gene Panel, Varies

Clinical Information: Lysosomal storage diseases (LSD) encompass a group of over 40 inherited biochemical diseases in which genetic variants cause defective lysosomal functioning. Lysosomes perform catabolic functions for cells, which is accomplished through activity of various proteins such as lysosomal enzymes, transport proteins, and other proteins. Functional deficits in these proteins cause an accumulation of substrates in cells leading to progressive organ dysfunction. This leads to variable clinical features that can affect the cardiovascular, neurological, ocular, and skeletal systems, among others. Clinical features are dependent on the amount and location of the substrate accumulation but may include the following: characteristic facial features (coarse features), hepatomegaly, deafness, vision loss, abnormal skeletal findings, hydrops fetalis, ataxia, hypotonia, developmental delay/regression, and intellectual disability. Age of onset is variable, with symptoms presenting from the prenatal period to adulthood, but generally LSD are progressive and cause significant morbidity and mortality with a decreased lifespan. Enzyme replacement therapy and oral substrate inhibitors are therapeutic options for some LSD. LSD are inherited in an autosomal recessive manner with the exception of Hunter, Fabry, and Danon diseases, which are X-linked. There are founder variants associated with particular LSD in the Ashkenazi Jewish and Finnish populations, leading to an increased carrier frequency for some. Overall, the prevalence of LSD is estimated at 1 in 7000 to 1 in 8000. Neuronal ceroid lipofuscinoses (NCL) are a subset of LSD that involve defective cellular processing of lipids. NCL are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophilic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles (FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms. Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult onset form (ANCL; DNAJC5 gene) has been shown to be autosomal dominant. This panel includes sequencing of 43 genes related to various LSD, as well as 15 genes specific to NCL. Alterations in various genes on this panel have also been associated with Parkinson disease or Lewy body disease. These alterations are not reported for individuals younger than 18 years of age but are available upon request.

Useful For: Follow up for abnormal biochemical results and confirmation of suspected lysosomal storage disease (LSD) Establishing a molecular diagnosis for patients with LSD Identifying variants within genes known to be associated with LSD, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Lysosomal Storage Disease Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Lysosomal Storage Disorders Screen, Random, Urine

Clinical Information: Lysosomal storage disorders (LSD) are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules leading to cell damage and organ dysfunction. Approximately 50 LSD have been described with a wide phenotypic spectrum and ranging in severity from neonatal lethal to later onset milder variants. Although classification is not always straightforward, LSD are generally categorized according to the type of storage material that accumulates in the cells and tissues. Major categories include mucopolysaccharidoses, oligosaccharidoses, mucolipidoses, and sphingolipidoses. In many cases, accumulating analytes can be detected in urine. Screening for these disorders typically begins with an analysis to detect disease-specific metabolite patterns or profiles indicative of a LSD. The combined analysis of disease-specific markers for LSD in multiple tests can allow for the identification of additional disorders that may not be picked up using any of the single tests alone. Disorders detectable by this approach include the oligosaccharidoses: alpha-mannosidosis, aspartylglucosaminuria, fucosidosis, Schindler disease, and sialidosis; the sphingolipidoses: GM1 gangliosidosis, Sandhoff disease, galactosialidosis, saposin B deficiency, metachromatic leukodystrophy, multiple sulfatase deficiency, Fabry disease, Gaucher disease, and Krabbe disease; the mucopolysaccharidoses excluding MPS IX (hyaluronidase deficiency); the glycogen storage disorder Pompe disease and the mucolipidoses types II and III. Additionally, other disorders such as congenital disorder of glycosylation (CDG) type IIb, and deglycosylation disorders such as NGLY1-CDG may also be detected. The mucopolysaccharidoses (MPS) are a subset of lysosomal storage disorders caused by the deficiency of any one of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. The oligosaccharidoses (glycoproteinoses) are a subset of lysosomal storage disorders caused by the deficiency of any one of the lysosomal enzymes involved in the degradation of complex oligosaccharide chains. They are characterized by the abnormal accumulation of incompletely degraded oligosaccharides in cells and tissues and the corresponding increase of related free oligosaccharides in the urine. Clinical features can include bone abnormalities, coarse facial features, corneal cloudiness, organomegaly, muscle weakness, hypotonia, developmental delay, and ataxia. Age of onset ranges from early infancy to adult and can even present prenatally. The sphingolipidoses are a subset of lysosomal storage disorders caused by a defect in any one of the enzymes that degrade complex ceramide containing lipids. They are characterized by the excessive accumulation of...
sphingolipids in the tissues, particularly in the central nervous system resulting in progressive neurodegeneration and developmental regression. In 2 conditions, Fabry disease and Gaucher disease type I, there is only systemic involvement. In many cases, sphingolipidoses can be detected by through oligosaccharide analysis in urine. Because of the similarity of features across disorders and their phenotypic variability, clinical diagnosis of LSD can be challenging; therefore, the combined analysis of multiple urine screening tests is an important tool for the initial workup of an individual suspected of having a lysosomal storage disorder. Abnormal results can be followed up with the appropriate enzyme or molecular analysis.

**Useful For:** Screening patients suspected of having a lysosomal storage disorder

**Interpretation:** When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test). Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. Specific enzymatic or molecular assays is recommended to confirm positive results.

**Reference Values:**
An interpretive report will be provided.


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**LSD6W 606171**

**Lysosomal Storage Disorders, Six-Enzyme Panel, Leukocytes**

**Clinical Information:** Lysosomes are intracellular organelles containing hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher Disease: Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, acid beta-glucosidase (glucocerebrosidase) due to variants in the GBA gene. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucosylsphingosine (glucosylphosphoglycosine). Impaired enzyme activity results in accumulation of undegraded glucocerebrosides in the lysosome, resulting in organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease with varying presentations and age of onset, but all include hepatosplenomegaly and hematological abnormalities as symptoms. Gaucher disease type I is the most common, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system (CNS) involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease. In addition, type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and individuals may survive into the third and fourth decade of life. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and chaperone therapy for types 1 and 3 (type 3, subacute neuropathic/juvenile). Currently, only supportive therapy is available for type 2. The biomarker, glucosylsphingosine, is elevated in symptomatic individuals and supports a diagnosis of Gaucher disease (GPSY / Glucosylsphingosine, Blood Spot). Niemann-Pick disease type A and B: Niemann-Pick disease types A (NPA) and B (NPB) are caused by a deficiency of sphingomyelinase
The biomarkers globotriaosylsphingosine (LGBBS / Globotriaosylsphingosine, Blood Spot) and ceramide the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) are recommended to detect carriers. as many carriers have normal enzyme activity. Additional studies including molecular genetic analysis of measurement of GLA activity is not generally useful for identifying female patients with Fabry disease, of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. the fourth decade. The cardiac variant is not associated with renal failure. Female patients who are carriers symptoms with the classic form of Fabry disease. Individuals with the renal variant are often acroparesthesias (pain crises), multiple angiokeratomas, reduced or and, to a lesser degree, brain. NPA is more severe than NPB and is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. NPB is limited to visceral symptoms with survival into adulthood. Some individuals have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Both NPA and NPB are caused by variants in the SMPD1 gene. Individuals with NPA and NPB typically have elevation of the oxysterol, lyso-sphingomyelin (LSM); cholestane-3 beta, 5 alpha, 6 beta-triol (COT) or 7-ketocholesterol (7-KC) may also be elevated. For more information see OXYBS / Oxysterols, Blood Spot. Pompe Disease: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to variants in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and eventually, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. Because Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, in particular the juvenile and adult-onset forms, is often considered late, if at all, during the evaluation of individuals presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment with enzyme replacement therapy is available making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Krabbe Disease: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of the enzyme, galactocerebrosidase (GALC), due to variants in the GALC gene. GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide and lactosylsphingosine). In individuals with Krabbe disease, reduced GALC activity results in impaired degradation of these substrates, causing severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, has shown variable benefit. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A have been found. Saposin A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. The biomarker, psychosine (PSY / Psychosine, Blood Spot) has been shown to be elevated in individuals with active Krabbe disease. Fabry Disease: Fabry disease, caused by alterations in the GLA gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Male patients with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acropaesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occurs in middle age. Male patients with more than 1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of GLA activity is not generally useful for identifying female patients with Fabry disease, as many carriers have normal enzyme activity. Additional studies including molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) are recommended to detect carriers. The biomarkers globotriaosylsphingosine (LGBBS / Globotriaosylsphingosine, Blood Spot) and ceramide
trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in individuals with Fabry disease and may aid in the diagnostic evaluation of female patients. Mucopolysaccharidosis I: Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The mucopolysaccharides, heparan sulfate and dermatan sulfate, are elevated in affected individuals (MPSBS / Mucopolysaccharidosis, Blood Spot) and support a diagnosis of MPS I. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. MPS I is caused by variants in the IDUA gene and has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy.

**Useful For:** Diagnosis of the lysosomal storage disorders: Fabry (in male patients), Gaucher, Krabbe, mucopolysaccharidosis I (MPS I), Niemann-Pick types A and B, and Pompe (glycogen storage disorder type II) This test is not intended for carrier detection

**Interpretation:** Values below the reference ranges are consistent with a diagnosis of lysosomal storage disorders. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
- Beta-Glucosidase: > or =3.53 nmol/hour/mg protein
- Acid Sphingomyelinase: > or =0.32 nmol/hour/mg protein
- Acid Alpha-Glucosidase: > or =5.00 nmol/hour/mg protein
- Galactocerebrosidase: > or =1.88 nmol/hour/mg protein
- Alpha-Galactosidase: > or =10.32 nmol/hour/mg protein
- Alpha-L-Iduronidase: > or =2.06 nmol/hour/mg protein
- Acid Alpha-Glucosidase (Reflex): > or =1.50 nmol/hour/mg protein
- Galactocerebrosidase (Reflex): > or =0.30 nmol/hour/mg protein

An interpretative report will be provided.

**Clinical References:**

**Lysozyme (LYZ) Gene, Full Gene Analysis, Varies**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are...
a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis, including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, fibrinogen alpha chain, gelsolin, cystatin C and lysozyme. Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Lysozyme (LYZ) gene-related familial visceral amyloidosis presents clinically with significant renal impairment. The renal dysfunction occurs at an early age and, in the absence of treatment, results in renal failure. Other manifestations of LYZ-related familial visceral amyloidosis include gastrointestinal involvement, cardiac disease, Sicca syndrome, and propensity towards petechiae, hemorrhage and hematoma, including hepatic hemorrhage. The bleeding tendency associated with LYZ-related familial visceral amyloidosis has included rupture of abdominal lymph nodes. Neuropathy is not a feature of LYZ-related familial visceral amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Confirming a diagnosis of lysozyme (LYZ) gene-related familial visceral amyloidosis

This test is not useful for assessment of lysozyme levels.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Lysozyme (Muramidase), Plasma**

**Clinical Information:** Lysozyme is a bacteriolytic enzyme that is found in some hematopoietic cells. It is primarily present in granulocytes, monocytes, and histiocytes. The enzyme is present in only minute amounts in lymphocytes; and is not present in myeloblasts, eosinophils, and basophils. Lysozyme in the plasma comes chiefly from the degradation of granulocytes and monocytes and its concentration reflects the turnover of these cells. Increases are seen in benign (e.g., infection, inflammation) and malignant processes (e.g., some leukemias). Plasma lysozyme is elevated in patients with acute or chronic granulocytic or mononuclear leukemias and falls with successful treatment. Conversely, patients with lymphocytic leukemia may have depressed plasma lysozyme levels. Patients with renal disorders (including rejection of transplanted kidneys) or Crohn disease (regional enteritis) also tend to have elevated levels of plasma lysozyme.

**Useful For:** As a screening test for ocular sarcoidosis Confirming marked increases in the granulocyte or monocyte pools as in granulocytic or mononuclear leukemias, myeloproliferative disorders, and malignant histiocytosis Following the course of therapy in cases of chronic granulocytic or chronic mononuclear leukemias

**Interpretation:** Levels above 200 mcg/mL may be seen in acute nonlymphocytic leukemia (M2, M4,
M5) or chronic granulocytic leukemias.

**Reference Values:**

> or =12 months: 2.6-6.0 mcg/mL

Reference values have not been established for patients who are less than 12 months of age.

**Clinical References:**


**LYSOZ**

**Lysozyme Immunostain, Technical Component Only**

**Clinical Information:** Lysozyme is an intracellular enzyme found in the primary granules of myeloid cells, monocytes, and histiocytes. Diagnostically, antibodies to lysozyme can help confirm monocytic and histiocytic differentiation in acute myeloid leukemia or histiocytic sarcoma.

**Useful For:** Aids in confirmation of monocytic and histiocytic differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


**LYSO**

**Lysozyme, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing the diagnosis of an allergy to lysozyme. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**M-Protein Isotype, Matrix-Assisted Laser Desorption-Ionization Time-of-Flight Mass Spectrometry, Serum**

**Clinical Information:** Immunotyping of monoclonal (M-) proteins identifies the monoclonal immunoglobulin heavy chain type (gamma, alpha, mu, delta, or epsilon) and light chain type (kappa or lambda) in serum specimens.

**Useful For:** Aiding in the diagnosis of monoclonal gammopathies, when used in conjunction with free light chain studies. This test alone is not considered an adequate screen for monoclonal gammopathies.

**Interpretation:** A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic protein electrophoresis pattern is suggestive of a possible monoclonal protein. Immunoaffinity purification followed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify the immunoglobulin heavy and light chains.

**Reference Values:** Negative: No monoclonal protein detected.

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic diseases, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children under 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to macadamia nut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to mackerel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

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*Reference values apply to all ages.*


**Mackerel, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6 &gt;=100</td>
<td>Strongly positive</td>
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</tbody>
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Reference values apply to all ages.


**Macroamylase**

**Reference Values:**

Not Detected

**Macroprolactin, Serum**

**Clinical Information:** Prolactin is secreted by the anterior pituitary gland under negative control by dopamine, which is secreted by the hypothalamus. The only physiological function of prolactin is the stimulation of milk production. In normal individuals, the prolactin concentration in blood rises in response to physiologic stimuli such as nipple stimulation, sleep, exercise, sexual intercourse, and hypoglycemia. Certain medications, (eg, phenothiazines, metoclopramide, risperidone, selective serotonin reuptake inhibitors, estrogens, verapamil) may also cause hyperprolactinemia. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma), diseases of the hypothalamus, primary hypothyroidism, section compression of the pituitary stalk, chest wall lesions, renal failure, and ectopic tumors. Hyperprolactinemia may also be caused by the presence of a high-molecular-mass complex of prolactin called macroprolactin (typically due to prolactin bound to immunoglobulin). In this situation, the patient is asymptomatic. Hyperprolactinemia attributable to macroprolactin is a frequent cause of misdiagnosis and mismanagement of patients. Macroprolactin should be considered if, in the presence of elevated prolactin levels, signs and symptoms of hyperprolactinemia are absent, or pituitary imaging studies are not informative.

**Useful For:** Determining biologically active levels of prolactin, in asymptomatic patients with elevated prolactin levels Ruling out the presence of macroprolactin

**Interpretation:** When the fraction (percentage) of polyethylene glycol (PEG)-precipitated (complexed) prolactin is 60% or less of total prolactin, the specimen is considered negative for
When total prolactin exceeds the upper reference limit and macroprolactin is negative, other causes for hyperprolactinemia should be explored. When the fraction (percentage) of polyethylene glycol (PEG)-precipitated (complexed) prolactin is above 60%, the specimen is considered positive for the presence of macroprolactin. Following polyethylene glycol (PEG)-precipitation, a patient whose unprecipitated prolactin concentration is greater than the upper limit of the unprecipitated prolactin reference interval may have hyperprolactinemia. See PRL / Prolactin, Serum for interpretation of prolactin levels.

**Reference Values:**

**PROLACTIN, TOTAL**

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<th>Age</th>
<th>Reference Interval</th>
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<tr>
<td></td>
<td>&gt; or =18 years</td>
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</tr>
<tr>
<td>Females</td>
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</tr>
<tr>
<td></td>
<td>&gt; or =18 years</td>
<td>4.8-23.3 ng/mL</td>
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</tbody>
</table>

**PROLACTIN, UNPRECIPITATED**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>&lt;18 years</td>
<td>not established</td>
</tr>
<tr>
<td></td>
<td>&gt; or =18 years</td>
<td>2.7-13.1 ng/mL</td>
</tr>
<tr>
<td>Females</td>
<td>&lt;18 years</td>
<td>not established</td>
</tr>
<tr>
<td></td>
<td>&gt; or =18 years</td>
<td>3.4-18.5 ng/mL</td>
</tr>
</tbody>
</table>

When the percent of the precipitated (complexed) prolactin fraction of the total prolactin is 60% or less, the result is considered negative for macroprolactin.

**Clinical References:**


**Magnesium, 24 Hour, Urine**

**Clinical Information:** Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder are involved in intermediary metabolic processes; about 70% are present in free form, while the other 30% are bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct. Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys’ ability to excrete it, or a combination of the 2. Magnesium is an inhibitor of calcium crystal growth and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

**Useful For:** Assessing the cause of abnormal serum magnesium concentrations using a 24-hour urine
collection Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk

**Interpretation:** Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium greater than 24 mg/day or fractional excretion greater than 0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

**Reference Values:**
51-269 mg/24 hours
Reference values have not been established for patients <18 years and >83 years of age.

**Clinical References:**

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**Magnesium, Feces**

**Clinical Information:** The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl (1). Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars.(1) There are multiple potential causes of osmotic diarrhea. Measurement of magnesium in liquid stool can assist in identifying intentional or inadvertent use of magnesium and/or phosphate containing laxatives as the cause.(2-4) The other causes of osmotic diarrhea include ingestion of osmotic agents such as sorbitol or polyethylene glycol laxatives, or carbohydrate malabsorption due most commonly to lactose intolerance. Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6).(5,6)

**Useful For:** Workup of cases of chronic diarrhea Identifying the use of magnesium-containing laxatives contributing to osmotic diarrhea

**Interpretation:** Magnesium-induced diarrhea should be considered if the osmotic gap is above 75 mOsm/kg and is likely if the magnesium concentration is above 110 mg/dL.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**
Magnesium, Plasma

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems including all adenosine triphosphate (ATP)-dependent enzymatic reactions. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The plasma magnesium level is kept constant within very narrow limits. Regulation takes place mainly via the kidneys, primarily via the ascending loop of Henle. Conditions that interfere with glomerular filtration result in retention of magnesium and, hence, elevation of plasma concentrations. Hypermagnesemia is found in acute and chronic renal failure, magnesium overload, and magnesium release from the intracellular space. Mild-to-moderate hypermagnesemia may prolong atrioventricular conduction time. Magnesium toxicity may result in central nervous system (CNS) depression, cardiac arrest, and respiratory arrest. Preeclampsia patients may be treated with magnesium sulfate and monitoring magnesium levels may be initiated, however, in most cases, monitoring clinical signs (respiratory rate and deep tendon reflexes) is adequate and magnesium levels are not required. Numerous studies have shown a correlation between magnesium deficiency and changes in calcium, potassium, and phosphate homeostasis, which are associated with cardiac disorders such as ventricular arrhythmias that cannot be treated by conventional therapy, increased sensitivity to digoxin, coronary artery spasms, and sudden death. Additional concurrent symptoms include neuromuscular and neuropsychiatric disorders. Conditions that have been associated with hypomagnesemia include chronic alcoholism, childhood malnutrition, lactation, malabsorption, acute pancreatitis, hypothyroidism, chronic glomerulonephritis, aldosteronism, and prolonged intravenous feeding.

Useful For: Monitoring preeclampsia patients being treated with magnesium sulfate

Interpretation: Symptoms of magnesium deficiency do not typically appear until plasma levels are 1.0 mg/dL or lower. Plasma levels of 9.0 mg/dL or higher may be life-threatening.

Reference Values:
- 0-2 years: 1.6-2.7 mg/dL
- 3-5 years: 1.6-2.6 mg/dL
- 6-8 years: 1.6-2.5 mg/dL
- 9-11 years: 1.6-2.4 mg/dL
- 12-17 years: 1.6-2.3 mg/dL
- >17 years: 1.7-2.3 mg/dL


Magnesium, Random, Urine

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder are involved in intermediary metabolic processes; about 70% are present in free form, while the other 30% are bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct.(1) Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can
cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys' ability to excrete it, or a combination of the two.(2) Magnesium is an inhibitor of calcium crystal growth, and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

**Useful For:** Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk from a random urine collection

**Interpretation:** Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium greater than 24 mg/day or fractional excretion greater than 0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile, Random, Urine.

1 month-<12 months: 0.10-0.48 mg/mg creat
12 months-<24 months: 0.09-0.37 mg/mg creat
24 months-<3 years: 0.07-0.34 mg/mg creat
3 years-<5 years: 0.07-0.29 mg/mg creat
5 years-<7 years: 0.06-0.21 mg/mg creat
7 years-<10 years: 0.05-0.18 mg/mg creat
10 years-<14 years: 0.05-0.15 mg/mg creat
14 years-<18 years: 0.05-0.13 mg/mg creat
18 years-83 years: 0.04-0.12 mg/mg creat

Reference values have not been established for patients who are less than 1 month of age. Reference values have not been established for patients who are greater than 83 years of age.

**Clinical References:**

**Magnesium, Serum**

**Clinical Information:** Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate (ATP)-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Regulation takes place mainly via the kidneys, primarily via the ascending loop of Henle. Conditions that interfere with glomerular filtration result in retention of magnesium and, hence, elevation of serum concentrations. Hypermagnesemia is found in acute and chronic renal failure, magnesium overload, and magnesium release from the intracellular space. Mild-to-moderate hypermagnesemia may prolong atrioventricular conduction time. Magnesium toxicity may result in central nervous system (CNS) depression, cardiac arrest, and respiratory arrest. Numerous studies have shown a correlation between magnesium deficiency and changes in calcium, potassium, and phosphate homeostasis, which are associated with cardiac disorders such as ventricular arrhythmias that cannot be treated by conventional therapy, increased sensitivity to
digoxin, coronary artery spasms, and sudden death. Additional concurrent symptoms include neuromuscular and neuropsychiatric disorders. Conditions that have been associated with hypomagnesemia include chronic alcoholism, childhood malnutrition, lactation, malabsorption, acute pancreatitis, hypothyroidism, chronic glomerulonephritis, aldosteronism, and prolonged intravenous feeding.

**Useful For:** Monitoring preeclampsia patients being treated with magnesium sulfate, although in most cases monitoring clinical signs (respiratory rate and deep tendon reflexes) is adequate and blood magnesium levels are not required

**Interpretation:** Symptoms of magnesium deficiency do not typically appear until levels are 1.0 mg/dL or lower. Levels of 9.0 mg/dL or higher may be life-threatening.

**Reference Values:**
- 0-2 years: 1.6-2.7 mg/dL
- 3-5 years: 1.6-2.6 mg/dL
- 6-8 years: 1.6-2.5 mg/dL
- 9-11 years: 1.6-2.4 mg/dL
- 12-17 years: 1.6-2.3 mg/dL
- >17 years: 1.7-2.3 mg/dL

**Clinical References:**

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**Magnesium/Creatinine Ratio, Random, Urine**

**Clinical Information:** Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder are involved in intermediary metabolic processes; about 70% are present in free form, while the other 30% are bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct.(1) Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys' ability to excrete it, or a combination of the two.(2) Magnesium is an inhibitor of calcium crystal growth and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

**Useful For:** Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk.

**Interpretation:** Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium above 24 mg/day or fractional excretion above 0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary
magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

**Reference Values:**

- 1 month-<12 months: 0.10-0.48 mg/mg creat
- 12 months-<24 months: 0.09-0.37 mg/mg creat
- 24 months-<3 years: 0.07-0.34 mg/mg creat
- 3 years-<5 years: 0.07-0.29 mg/mg creat
- 5 years-<7 years: 0.06-0.21 mg/mg creat
- 7 years-<10 years: 0.05-0.18 mg/mg creat
- 10 years-<14 years: 0.05-0.15 mg/mg creat
- 14 years-<18 years: 0.05-0.13 mg/mg creat
- 18 years-83 years: 0.04-0.12 mg/mg creat

Reference values have not been established for patients who are less than 1 month of age. Reference values have not been established for patients who are greater than 83 years of age.

**Clinical References:**


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**FMME**

**Mahi Mahi IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.48 Equivocal/Borderline 2 0.49 – 0.99 Low Positive 3 1.00 – 1.99 Moderate Positive 4 2.00 – 3.49 High Positive 5 3.50 – 17.49 Very High Positive 6 >17.49 Very High Positive

**Reference Values:**

<0.35 kU/L

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**MALI**

**MAL Immunostain, Technical Component Only**

**Clinical Information:** MAL is a nonglycosylated hydrophobic integral membrane protein that forms, stabilizes, and maintains glycosphingolipid-enriched membrane microdomains. MAL is known also as T lymphocyte maturation-associated protein. MAL expression is a specific marker of primary mediastinal large B-cell lymphoma (PMBL).

**Useful For:** Diagnosis of primary mediastinal large B-cell lymphoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Malaria PCR with Parasitemia Reflex, Varies

**Clinical Information:** Malaria is a mosquito-transmitted disease caused by apicomplexan parasites in the genus Plasmodium. It is an important cause of morbidity and mortality worldwide, with the World Health Organization (WHO) estimating 219 million cases and 435,000 malaria-related deaths in 2017. Malaria disproportionately affects individuals living in Africa (90% of cases), with individuals living in southeast Asia and the eastern Mediterranean regions next most affected. Malaria is also encountered outside of endemic regions such as the United States, usually in returning travelers. Malaria is caused primarily by 4 species of the protozoa Plasmodium: P falciparum, P vivax, P malariae, and P ovale. A fifth Plasmodium species, P knowlesi, is a simian parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and species identification of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform specification by microscopy. Finally, Babesia parasites have a similar appearance to P falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. PCR is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias, and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment.

**Useful For:** Detection of Plasmodium DNA and identification of the infecting species, with reflex percent parasitemia calculated using thin blood films for positive cases. An adjunct to conventional microscopy of Giemsa-stained films. Detection and confirmatory identification of Plasmodium species: P falciparum, P vivax, P ovale, P malariae, and P knowlesi

**Interpretation:** A positive result indicates the presence of Plasmodium nucleic acid and melting curve analysis indicates the infecting species.

**Reference Values:**
Negative

If positive, percent parasitemia will be calculated and reported.

**Clinical References:**
ovale. A fifth Plasmodium species, P knowlesi, is a simian parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform species identification by microscopy. Finally, Babesia parasites have a similar appearance to P falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. PCR is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias, and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment. This test does not include blood smear examination or calculation of parasitemia.

**Useful For:** Detection of Plasmodium DNA and identification of the infecting species. An adjunct to conventional microscopy of Giemsa-stained films, particularly in cases of low percent parasitemia or suboptimal parasite morphology. Detection and confirmatory identification of Plasmodium species: P falciparum, P vivax, P ovale, P malariae, and P knowlesi. This test should not be used to screen asymptomatic patients.

**Interpretation:** A positive result indicates the presence of Plasmodium nucleic acid and melting curve analysis indicates the infecting species.

**Reference Values:**
Negative

**Clinical References:**

**Malaria/Babesia Percent Parasitemia Reflex, Varies**

**Clinical Information:** Malaria and babesiosis are potentially life-threatening diseases caused by Plasmodium and Babesia species respectively. Diagnosis of both infections is traditionally performed by microscopic examination of Giemsa-stained thick and thin blood films. However, malaria or Babesia PCR can also be used for sensitive and specific detection. When positive, PCR results for either organism should be followed by calculation of percent parasitemia from blood film examination. The degree of parasitemia is used to predict prognosis as well as monitor response to treatment for patients with malaria and babesiosis.

**Useful For:** Only orderable as a reflex. For more information see LMALP / Malaria PCR with Parasitemia Reflex. Calculation of percent parasitemia that can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis.

**Interpretation:** The percentage parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Plasmodium gametocytes are
not included in the calculation since they are not infectious to humans and are not killed by most antimalaria drugs.

**Reference Values:**
Only orderable as a reflex. For more information see LMALP / Malaria PCR with Parasitemia Reflex.

A percent parasitemia is provided following a positive result for LMALP / Malaria PCR with Parasitemia Reflex.

**Clinical References:**

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**MAAN**

**Maleic Anhydride, IgE, Serum**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to maleic anhydride Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>
Malignant Cells Cyto/Heme (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Malt, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to malt Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

MAML2 (11q21) Rearrangement, Mucoepidermoid Carcinoma (MEC), FISH, Tissue

Clinical Information: Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland neoplasm, representing over 30% of all malignant salivary gland tumors. The diagnosis of MEC can be quite challenging due to the degree of histologic overlap with other glandular, clear cell, or oncocytic salivary gland tumors. MAML2 rearrangements are detectable in 80% to 85% of MEC, but not in morphologic mimics such as oncocytic cystadenoma, Warthin tumor, oncocytoma, oncocytic carcinoma, acinic cell carcinoma, and metastatic renal cell carcinoma.

Useful For: Supporting a diagnosis of mucoepidermoid carcinoma

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the MAML2 probe. A positive result is consistent with a diagnosis of mucoepidermoid carcinoma (MEC). A negative result suggests no rearrangement of the MAML2 gene region at 11q21. However, this result does not exclude the diagnosis of MEC.

Reference Values: An interpretive report will be provided.


Mammaglobin (MGB) Immunostain, Technical Component Only

Clinical Information: Mammaglobin, a mammary specific member of the uteroglobin family, is known to be overexpressed in human breast cancer. It may be valuable when used in a panel with GCDFP-15 and ER to evaluate tumors of unknown primary site.

Useful For: Breast-specific marker Aids in evaluating tumors of unknown primary site

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to mandarin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
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<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Manganese, 24 Hour, Urine

Clinical Information: Manganese (Mn) is a trace essential element with many industrial uses. Mining and iron and steel production have been implicated as occupational sources of exposure. It is principally used in steel production to improve hardness, stiffness, and strength. Mn is a normal constituent of air, soil, water, and food. The primary non-occupational source of exposure is by eating food or Mn-containing nutritional supplements. Vegetarians who consume foods rich in Mn such as grains, beans, and nuts, as well as, heavy tea drinkers may have a higher intake than the average person. People who smoke tobacco or inhale second-hand smoke are also exposed to Mn at higher levels than non-smokers. Inhalation is the primary source of entry for Mn, but is also partially absorbed (3%-5%) through the gastrointestinal tract. Only very small amounts of Mn are absorbed dermally. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Mn toxicity is generally recognized...
to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgement, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthri an axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Mn is removed from the blood by the liver where it's conjugated with bile and excreted. As listed in the United States National Agriculture Library, Mn adequate intake is 1.6 to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of manganese than other food types. Patients on a long-term parenteral nutrition should receive manganese supplementation and should be monitored to ensure that circulatory levels of manganese are appropriate.

Useful For: Monitoring manganese exposure in 24 hour urine collections
Nutritional monitoring

Interpretation: Manganese (Mn) in urine represents the excretion of excess Mn from the body. Elevated levels may indicate occupational exposure or excessive nutritional intake. Specimens from normal individuals have very low levels of Mn.

Reference Values:
<4.0 mcg/specimen
Reference values have not been established for patients that are <18 years of age.


Manganese, Blood
Clinical Information: Manganese (Mn) is a trace essential element with many industrial uses. Mining and iron and steel production have been implicated as occupational sources of exposure. It is principally used in steel production to improve hardness, stiffness, and strength. Mn is a normal constituent of air, soil, water, and food. The primary non-occupational source of exposure is by eating food or Mn-containing nutritional supplements. Vegetarians who consume foods rich in Mn such as grains, beans, and nuts, as well as, heavy tea drinkers may have a higher intake than the average person. People who smoke tobacco or inhale second-hand smoke are also exposed to Mn at higher levels than non-smokers. Inhalation is the primary source of entry for Mn, but is also partially absorbed (3%-5%) through the gastrointestinal tract. Only very small amounts of Mn are absorbed dermally. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Mn toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgement, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthri an axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Mn is removed from the blood by the liver where it's conjugated with bile and excreted. The major compartment for circulating Mn is the erythrocytes, bound to hemoglobin, with whole blood concentrations of Mn (in patients with normal levels) being 10 times that of the serum. Mn passes from the blood to the tissues quickly. Concentrations in the liver are highest, with 1 to 1.5 mg Mn/kg (wet weight) in normal individuals. The half-life of Mn in the body is about 40 days, with elimination primarily through the feces. Only small amounts are excreted in the urine. Elevated levels of whole blood Mn have been reported, with and without central nervous system (CNS) symptoms, in patients with hepatitis B virus-induced liver cirrhosis, in patients on total parenteral nutrition (TPN) with Mn supplementation, and in infants born to mothers who were on TPN. The studies in cirrhotic patients with extrapyramidal symptoms indicate a possible correlation between whole blood Mn and that measured
by T1-weighted magnetic resonance in the globus pallidus and midbrain, with whole blood Mn levels
being 2-fold or more, higher than normal. Increases in whole blood Mn over time may be indicative of
future CNS effects. The data on TPN patients is based on anecdotes or small studies and is highly
variable, as is that obtained in infants.(2) Behcet disease, a form of chronic systemic vasculitis, has been
reported to exhibit 4-fold increase in erythrocyte Mn and it is suggested that increased activity of
superoxide dismutase may contribute to the pathogenesis of the disease. Mn has also been reported as a
contaminant in "garage" preparations of the abused drug methcathamine. Continued use of the drug
gives rise to CNS toxicity typical of manganism.(3) For monitoring therapy, whether of environmental
exposure, TPN, or cirrhosis, whole blood levels have been shown to correlate well with
neuropsychological improvement, although whether the laboratory changes precede the CNS or merely
track with them is unclear as yet. It is recommended that both CNS functional testing and laboratory
evaluation be used to monitor therapy of these patients. Long-term monitoring of Behcet disease has not
been reported, and it is not known if the Mn levels respond to therapy.

**Useful For:** Evaluation of central nervous system symptoms similar to Parkinson disease in manganese
(Mn) miners and processors Characterization of liver cirrhosis Therapeutic monitoring in treatment of
cirrhosis, parenteral nutrition-related Mn toxicity and environmental exposure to Mn Evaluation of Behcet
disease

**Interpretation:** Whole blood levels above the normal range are indicative of manganism (Mn). Values
between 1 and 2 times the upper limit of normal may be due to differences in hematocrit and normal
biological variation, and should be interpreted with caution before concluding that hypermanganesemia is
contributing to the disease process. Values greater than twice the upper limit of normal correlate with
disease. For longitudinal monitoring, sampling no more frequently than the half-life of the element (40
days) should be used.

**Reference Values:**
4.7-18.3 ng/mL

**Clinical References:**
1. Levy BS, Nassetta WJ: Neurologic effects of manganese in humans: A
Whole blood and red blood cell manganese reflected signal intensities of T1-weighted magnetic resonance
manganese concentrations in red blood cells of smelting workers: search for biomarkers of manganese
Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human
primates. Exp Neurol. 2006;202:381-390

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### Manganese, Red Blood Cell

**Reference Values:**

<table>
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<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manganese, Plasma</td>
<td>&lt;2.0 ng/mL</td>
</tr>
<tr>
<td>Manganese, RBC</td>
<td>11.0 - 23.0 ng/mL</td>
</tr>
</tbody>
</table>

Manganese is highly concentrated in the cellular elements of blood. Hemolysis of the cellular elements
that is unobservable to the naked eye can result in elevated plasma manganese concentrations.

### Manganese, Serum

**Clinical Information:** Manganese (Mn) is a trace essential element with many industrial uses.
Mining and iron and steel production have been implicated as occupational sources of exposure. It is
principally used in steel production to improve hardness, stiffness, and strength. Mn is a normal
constituent of air, soil, water, and food. The primary non-occupational source of exposure is by eating
food or Mn-containing nutritional supplements. Vegetarians who consume foods rich in Mn such as
grains, beans, and nuts, as well as, heavy tea drinkers may have a higher intake than the average person.
People who smoke tobacco or inhale second-hand smoke are also exposed to Mn at higher levels than non-smokers. Inhalation is the primary source of entry for Mn, but is also partially absorbed (3%-5%) through the gastrointestinal tract. Only very small amounts of Mn are absorbed dermally. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Mn toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthrian axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Mn is removed from the blood by the liver where it's conjugated with bile and excreted. As listed in the United States National Agriculture Library, Mn adequate intake is 1.6 to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of Mn than other food types. Patients on a long-term parenteral nutrition should receive Mn supplementation and should be monitored to ensure that circulatory levels of Mn are appropriate.

**Useful For:** Monitoring manganese exposure using serum specimens Nutritional monitoring

**Interpretation:** Serum manganese results above the reference values suggest recent exposure.

**Reference Values:**
<2.4 ng/mL

Reference values have not been established for patients that are <18 years of age.

**Clinical References:**

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**Manganese/Creatinine Ratio, Random, Urine**

**Clinical Information:** Manganese (Mn) is an essential trace element with many industrial uses. Manganese is the 12th most abundant element in the earth's crust and is used predominantly in the production of steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly or not at all; neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthrian axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Few cases of manganese deficiency or toxicity due to ingestion have been documented. Only 1% to 3% manganese is absorbed via ingestion, while most of the remaining manganese is excreted in the feces. As listed in the United States National Agriculture Library, manganese adequate intake is 1.6 to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of manganese than other food types. Patients on a long-term parenteral nutrition should receive manganese supplementation and should be monitored to ensure that circulatory levels of manganese are appropriate.

**Useful For:** Monitoring manganese exposure Nutritional monitoring Clinical trials

**Interpretation:** Manganese in urine represents the excretion of excess manganese from the body,
and may be used to monitor exposure or excessive nutritional intake.

**Reference Values:**

<4.0 mcg/g creatinine  
Reference values have not been established for patients that are <18 years of age.


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**Mango, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to mango  
Defining the allergen responsible for eliciting signs and symptoms  
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
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<td>1</td>
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<tr>
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<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Mannan Binding Lectin (MBL)**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1634
Reference Values:
>100 ng/mL

Investigators most frequently use 100 ng/mL as the threshold for defining an MBL deficiency. MBL values below this value may be associated with increased susceptibility to infection.

**Mannose Binding Lectin**

**Clinical Information:** Mannose-binding protein is a component of the innate or natural immune system which binds to mannose residues on a variety of different microorganisms. When bound, this lectin will trigger the complement pathway resulting in opsonization. Mannose-binding protein is also an acute phase reactant produced by the liver. Patients who have abnormal levels of mannose-binding protein may have recurrent significant infections in the absence of abnormalities in the four major arms of the immune system. Abnormal mannose-binding protein concentrations have been found in patients with infectious disorders such as tuberculosis, hepatitis B, and in autoimmune disorders including recurrent spontaneous abortion and systemic lupus erythematos.

**Reference Values:**
Reference Interval: >50 ng/mL

**Maple Red (Acer rubrum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**Maple Syrup Urine Disease Gene Panel, Varies**

**Clinical Information:** Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). MSUD can be divided into 5 phenotypes: classic, intermediate, intermittent, thiamine-responsive, and dihydrodipropyl dehydrogenase (E3)-deficient, depending on the clinical presentation and response to thiamine administration. Classic MSUD, the most common and most severe form, presents in newborns with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor in urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Age of onset for individuals with non-classical forms of MSUD is variable, with some presenting with symptoms as early as 2 years of age. Symptoms include poor growth and feeding, irritability, and developmental delays. These patients can also experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress. MSUD is a panethnic condition but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1 in 760 live births. The incidence of MSUD is approximately 1 in 185,000 live births in the general population. A comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features given the broad clinical spectrum and genetic heterogeneity of MSUD. The BCKDH complex consists of 4 subunits (E1a, E1b, E2, E3), and this panel includes testing of the genes that encode each subunit (BCKDHA for E1a, BCKDHB for E1b, DBT for E2, and DLD for E3). In addition, BCKDK and PPM1K are also included, both of which impact the activity of the BCKDH complex. Pathogenic variants in both alleles of any of these genes result in disease. The recommended first-tier tests to screen for MSUD is a combination of biochemical tests including quantitative plasma amino acids (AAQP/ Amino Acids, Quantitative, Plasma) to measure BCAA levels and alloisoleucine and urine organic acids (OAU / Organic Acids Screen, Urine) to look for presence of toxic urine.
metabolites including 2-hydroxy-isovaleric acid and 2-oxo-isocaprioic acid. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and allo-isoleucine concentrations. Orthotopic liver transplantation has been successful and is an effective therapy for MSUD.

Useful For: Follow up for abnormal biochemical results suggestive of maple syrup urine disease (MSUD) Establishing a molecular diagnosis for patients with MSUD Identifying variants within genes known to be associated with MSUD, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

MAPTZ
MAPT Gene, Sequence Analysis, 7 Exon Screening Panel, Varies

Clinical Information: Frontotemporal dementia is a familial adult-onset, presenile dementia that affects the frontal and temporal cerebral cortices. Clinical presentation is variable and includes changes in behavior, difficulties with language, rigidity, palsy, and saccadic (rapid) eye movement. Symptoms generally begin between 40 and 60 years of age, with mean age of onset at approximately 45 years, and typically last between 5 and 10 years, progressing to severe dementia and mutism. The presentation of frontotemporal dementia may be confused with other dementias, including Alzheimer disease. It is important to distinguish between these different dementias because progression and patient management are different for the various dementias. Based on the immunohistochemical staining, there are 2 main subtypes of frontotemporal lobar degeneration (FTLD): tau-positive FTLD and tau-negative FTLD with ubiquitin-positive inclusions (FTLD-U). Mutations in the MAPT gene have been identified in patients with tau-positive FTLD; mutations in the progranulin gene (GRN) have been identified in patients with FTLD-U. Both MAPT and GRN are located on chromosome 17q21. The MAPT gene encodes the microtubule-associated tau protein. A number of mutations have been identified in the MAPT gene that result in aggregation of the tau protein. Although there is variable expression of disease presentation and severity within and between families, the hallmark neurologic lesion constitutes tau-positive protein inclusion bodies. Most clinically significant mutations are found in exons 9 through 13. Several intrinsic mutations, associated with alternative splicing of the mRNA, contribute to the variability of expression of the disease traits. Mutations in the MAPT gene have also been identified in cases of progressive supranuclear palsy, corticobasal degeneration, and dementia with epilepsy.

Useful For: Aiding in the diagnosis of frontotemporal dementia, progressive supranuclear palsy,
corticobasal degeneration, and dementia with epilepsy Distinguishing the diagnosis of frontotemporal dementia from other dementias, including Alzheimer dementia Identifying individuals who are at risk of frontotemporal dementia

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. All variants will be reported in reference to transcript NM_001123066 (build GRCh37 (hg19)).

**Reference Values:**
An interpretive report will be provided.


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**MARE 82141**

**Mare's Milk, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to mare's milk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
<table>
<thead>
<tr>
<th>Range</th>
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<td>Strongly positive</td>
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<tr>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
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</tbody>
</table>

Reference values apply to all ages.


Marfan Syndrome and Related Disorders Multi-Gene Panel, Varies

Clinical Information: Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and mitral valve prolapse and aortic root dilatation/dissection are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of FBN1. Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the FBN1 gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis). Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities, and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants of the SMAD3 gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants of the TGFBR3 gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity. TAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is ACTA2. For other genes also implicated in TAAD, refer to the table below. The COL3A1 gene causes Ehlers Danlos syndrome, vascular type (type IV), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously. The COL5A1 and COL5A2 genes cause Ehlers Danlos syndrome, classic type (type I and type II), an autosomal dominant connective tissue disorder characterized by skin hyperextensibility, widened atrophic scars, joint hypermobility, smooth, velvety skin, and easy bruising. The FLNA gene causes FLNA-related periventricular nodular heterotopia (PVNH), an X-linked neuronal migration disorder where the majority of affected individuals are female. This condition is characterized by seizures, hyperflexible joints, and cardiac findings, which include thoracic aortic aneurysm and dissection. Some individuals show clinical overlap with EDS. Autosomal dominant variants of the FBN2 gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm. Variants of the CBS gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting. Variants in the SKI gene cause...
Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS, but, when present, it can be severe. Homozygous and compound heterozygous loss of function variants in the SLC2A10 gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features. Variants in the NOTCH1 gene cause aortic valve disease, with individuals displaying a range of aortic valve abnormalities and severe valve calcification. Genes included in Marfan Syndrome and Related Disorders Multi-Gene Panel: Gene Protein Inheritance Known Association ACTA2 Actin, alpha-2, smooth muscle, aorta AD TAAD CBS Cystathionine beta-synthase AR Homocystinuria COL3A1 Collagen, type III, alpha-1 AD Ehlers-Danlos syndrome, vascular type (EDS type IV) COL5A1 Collagen, type V alpha-1 AD Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II) COL5A2 Collagen, type V alpha-2 AD Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II) FBN1 Fibrillin 1 AD Marfan syndrome/TAAD/Ectopia Lentis/MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome FBN2 Fibrillin 2 AD Congenital Contractual Arachnodactyly FLNA Filamin A X-linked Ehlers-Danlos syndrome and periventricular nodular heterotopia/X-linked cardiac valvular dysplasia/otopalatodigital spectrum disorders/TAAD MFAP5 Microfibril-associated protein 5 AD TAAD MYH11 Myosin, heavy chain 11, smooth muscle AD TAAD MYLK Myosin light chain kinase AD TAAD NOTCH1 Notch, drosophila, homolog of, 1 AD Aortic valve disease/Adams-Oliver Syndrome PRKG1 Protein kinase, cGMP-dependent, type 1 AD TAAD SKI V-SKI avian sarcoma viral oncogene homolog AD Shprintzen-Goldberg syndrome SLC2A10 Solute carrier family 2 (facilitated glucose transporter), member 10 AR Arterial Tortuosity syndrome/TAAD (Autosomal Recessive) SMAD3 Mothers against decapentaplegic, drosophila, homolog of, 3 AD Loey-Dietz syndrome/TAAD SMAD4 Mothers against decapentaplegic, drosophila, homolog of, 4 AD TAAD/IPS/IPS-HHT TGFBR2 Transforming growth factor, beta-2 AD TAAD TGFBR1 Transforming growth factor-beta receptor, type 1 AD Loey-Dietz syndrome/TAAD TGFBR2 Transforming growth factor-beta receptor, type II AD Loey-Dietz syndrome/TAAD Abbreviations: Autosomal dominant (AD), autosomal recessive (AR); thoracic aortic aneurysm and dissection (TAAD); juvenile polyposis syndrome (JPS); juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia (JPS-HHT) Indications for testing include but are not limited to: -Patients who meet clinical diagnostic criteria (Revised Ghent nosology) for Marfan syndrome -Patients in whom no specific Marfan or related disorder is evident but for whom there is a clear familial component -Patients whose family history is consistent with TAAD -Patients with a personal or family history of thoracic aortic aneurysm and/or dissection or a personal or family history of multiple arterial aneurysms

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome, Loey-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder Second-tier testing for patients in whom previous targeted gene variant analyses for specific Marfan and related genes were negative Establishing a diagnosis of a Marfan or a related disorder in some cases, allowing for appropriate management and surveillance for aneurysms and other disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for aneurysms and other disease features allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:** An interpretive report will be provided.


### Marjoram, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to marjoram Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
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Reference values apply to all ages.

### Clinical References:

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### MSPTC

**Mass Spectrometry (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

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### MATCC

**Maternal Cell Contamination, Molecular Analysis, Varies**

**Clinical Information:**
One of the risks associated with prenatal testing is maternal cell contamination (MCC), which can occur when a fetal specimen comes into contact with maternal blood or tissue. The risk of MCC is associated with procedures such as chorionic villus sampling, amniocentesis, or extraction of fetal blood from the umbilical cord (cord blood). If MCC is present, the maternal DNA may mask the results of any genetic testing performed on the fetal DNA. Therefore, the results of prenatal testing may be compromised. To rule out the presence of MCC, a maternal blood specimen is necessary for comparison of maternal and fetal chromosomal markers. The presence of both maternal and nonmaternal alleles for each fetal marker indicates the fetal specimen is not contaminated. MCC is confirmed when both alleles in the fetus are maternal.

**Useful For:** Ruling out the presence of maternal cell contamination within a fetal specimen
This test is required for all prenatal testing performed in Mayo's molecular and biochemical genetics laboratories

**Interpretation:**
An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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### FFMSS

**Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT**

**Clinical Information:**
This test combines a first- and second-trimester specimen to screen low-risk
pregnancies for Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18).
Collection of two blood samples is required for this test. A first trimester ultrasound to measure the fetal
nuchal translucency (NT) is optional (see special instructions). Patient demographics and
analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of
the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks of
ONTD, DS and T18. Markers used for assessment of risk include first-trimester PAPP-A with or
without NT and second-trimester AFP, hCG, unconjugated estriol (uE3) and dimeric Inhibin A. A DS
risk of 1 in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 87 percent
at a screen positive rate of 1.0%. A T18 risk of 1 in 100 or worse is reported as abnormal. This risk
cutoff predicts a detection rate of 90 percent at a screen positive rate of <0.5%. ARUP uses a singleton
AFP MoM cut off of $\geq 2.5$. If the interpretation is "high AFP," there is an increased risk of an
ONTD in the pregnancy. This cutoff value predicts a detection rate of 80% at a screen positive rate of
1.5%. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age.
Pregnancies at an increased risk for ONTD with an AFP MoM $< 2.5$, but a risk of 1 in 250 or worse, are
also reported as abnormal. This is usually due to a family history of ONTD, the use of certain seizure
medications by the patient during pregnancy, or the presence of maternal insulin-dependent diabetes,
any of which increases a patient's priori risk for ONTD. An increased risk of congenital steroid sulfatase
deficiency or Smith-Lemli-Opitz syndrome (uE3 $\leq 0.14$ MoM) and poor fetal outcome (hCG $>\geq 3.5$ MoM) is reported as "see note".

**Useful For:** Helpful to identify pregnancies at increased risk of having a child with Down Syndrome
(DS), open neural tube defects (ONTD) and trisomy 18 (T18). This test is not diagnostic.

**Interpretation:** The first specimen of an integrated Maternal Serum Screening is used to measure
PAPP-A. A second sample must be submitted for a final interpretive report. Acceptable date ranges to
draw the second samples will be provided in the Integrated-1 report. Final interpretive report will be
available when the second specimen test results are complete.

**Reference Values:**
An interpretive report will be provided.

Part 2 must be completed in order to receive an interpretable result.

If the second specimen is not received for sequential screening, the results are uninterpretable and no
maternal risk will be provided.
Smith-Lemli-Opitz syndrome (uE3 $\leq$0.14 MoM) and poor fetal outcome (hCG $\geq$3.5 MoM) is reported as "see note."

Useful For: Helpful to identify pregnancies at increased risk of having a child with Down syndrome (trisomy 21), Open Neural Tube Defect (ONTD, spina bifida) and trisomy 18 (T18). This test is not diagnostic. The patient information provided with the Integrated, Specm1 will be used to calculate the risks for this report.

Interpretation: An interpretive report will be provided. See clinical information sections. Part 2 must be completed in order to receive an interpretable result. If the second specimen is not received for sequential screening, the results are uninterpretable and no maternal risk will be provided.

Reference Values: An interpretive report will be provided.

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**MaterniT21 Plus**

**Clinical Information:** The MaterniT21 PLUS test analyzes circulating cell-free DNA extracted from a maternal blood sample. The test is indicated for use in pregnant women with increased risk for chromosomal aneuploidy. Validation data on twin pregnancies is limited and the ability of this test to detect aneuploidy in a triplet pregnancy has not yet been validated. DNA test results do not provide a definitive genetic risk in all individuals. Cell-free DNA does not replace the accuracy and precision of prenatal diagnosis with CVS or amniocentesis. These tests are not intended to identify pregnancies at risk for neural tube defects or ventral wall defects. A patient with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results. A negative test result does not ensure an unaffected pregnancy. While results of this testing are highly accurate, not all chromosomal abnormalities may be detected due to placental, maternal or fetal mosaicism, or other causes. The health care provider is responsible for the use of this information in the management of their patient.

Reference Values: A final report will be provided.

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**Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow**

**Clinical Information:** Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy (MSMRT) classifies patients into either standard or high-risk categories based on the results of 2 assays: plasma cell proliferation and FISH for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with multiple myeloma, which can assist in determining treatment and management decisions Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: An interpretive report will be provided. Patients are classified as high risk, or standard risk.

Reference Values: PLASMA CELL CLONALITY:
- Normal bone marrow
- No monotypic clonal plasma cells detected
DNA INDEX:
Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05


MayoComplete Solid Tumor Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration (FDA) for treatment of solid tumor malignancies. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Tumor mutational burden (TMB) and microsatellite instability (MSI) status are increasingly important biomarkers for determining effective immunotherapeutic treatment options for patients with solid tumors.(1,2) In addition to providing therapeutic insight, molecular profiling of tumors often provides prognostic and diagnostic information. Next-generation sequencing is an accurate, cost-effective method to identify variants across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue or cytology specimens to assess for Tier I and Tier II variants in 514 genes known to be associated with solid tumors.(3)

Useful For: Assisting in tumor profiling for diagnosis, predicting prognosis, and identifying targeted therapies for the treatment and management of patients with solid tumors Identifying somatic alterations including single nucleotide variants (SNV), small insertions/deletions (INDEL), gene amplifications, fusions, and splice variants in genes known to be associated with the tumorigenesis of solid tumors Assessment of microsatellite instability and tumor mutational burden status

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

Clinical References: 1. Subbiah V, Solit DB, Chan TA, Kurzrock R: The FDA approval of
**MDM2 (12q15) Amplification, Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor, FISH, Tissue**

**Clinical Information:** Differential diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor: The histological discrimination of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT) from lipoma can be diagnostically challenging. However, standard cytogenetic identification of ring and giant rod chromosomes strongly support the diagnosis of WDL/ALT. These abnormal chromosomes are mainly composed of amplified sequences derived from chromosome bands 12q13-15, and contain several amplified genes including MDM2, CPM, CDK4, and TSPAN31. MDM2 is amplified in greater than 99% of WDL, and up to 30% of other types of sarcomas. Differential diagnosis of osteosarcoma: The histological discrimination of parosteal or low grade central osteosarcoma from other morphologically similar, but clinically distinct entities, can be difficult. Amplification of genomic material derived from chromosome 12q13-15, which contains several genes including MDM2, has been shown to be a recurrent finding in a large proportion (67-100%) of parosteal and central low-grade osteosarcomas. Therefore, the detection of MDM2 gene amplification by fluorescence in situ hybridization (FISH) may be a useful adjunct to support a diagnosis of low-grade central or parosteal osteosarcoma in the proper histopathologic context. Amplifications of 12q13-15 (including MDM2) are less common in conventional high-grade osteosarcoma, estimated to occur in approximately of 5% to 10% of tumors.

**Useful For:** Supporting a diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor

**Interpretation:** Differential diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the MDM2 fluorescence in situ hybridization (FISH) probe (positive result). A positive result is consistent with amplification of the MDM2 gene locus (12q15) and supports the diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT). A negative result is consistent with absence of amplification of the MDM2 gene locus (12q15). However, negative results do not exclude the diagnosis of WDL/ALT. Amplification varies in individual tumors and among different cells in the same tumor. Differential diagnosis of osteosarcoma: A positive result is consistent with amplification of the MDM2 gene locus (12q15) and supports the diagnosis of parosteal osteosarcoma or low-grade central osteosarcoma. A negative result indicates an absence of amplification of the MDM2 gene locus (12q15). However, negative results do not exclude the diagnosis of low-grade central osteosarcoma or parosteal osteosarcoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Meadow Fescue, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceeds as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to meadow fescue Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Meadow Foxtail, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for...
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to meadow foxtail Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Measles (Rubeola) Antibodies, IgG, Serum**

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is one of the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreads centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to fewer than 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class
antibodies to measles virus will aid in identifying nonimmune individuals.

**Useful For:** Determination of immune status of individuals to the measles virus. Documentation of previous infection with measles virus in an individual without a previous record of immunization to measles virus.

**Interpretation:** Positive: Antibody index (AI) value of 1.1 or higher. The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies indicates prior exposure to the measles virus through infection or immunization. Individuals testing positive are considered immune to measles infection. Equivocal: AI value 0.9-1.0. Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value of 0.8 or lower. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus.

**Reference Values:**
Vaccinated: positive (> or =1.1 AI)
Unvaccinated: negative (< or =0.8 AI)
Reference values apply to all ages.

**Clinical References:**

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**Measles (Rubeola) Antibodies, IgM, Serum**

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours. Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.

Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to below 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States. (4) Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs. (5) The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection, but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus aids in identifying nonimmune individuals.

**Useful For:** Determining acute-phase infection with rubeola (measles) virus using IgM antibody testing. Aiding in the identification of nonimmune individuals through IgM antibody testing.

**Interpretation:** This assay tests only for IgM-class antibody. For both IgM and IgG antibody testing, see ROGM / Measles (Rubeola) Virus Antibody, IgM and IgG (Separate Determinations), Serum. The
presence of IgM-class antibodies, with or without the presence of IgG-class antibodies to measles virus may support a clinical diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase infection with measles virus. However serology may be negative for IgM-class antibodies in early disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class antibodies to measles should be limited to patients with clinically compatible disease. The presence of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the measles virus through infection or immunization. These individuals are considered immune to measles infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus. These individuals are considered nonimmune to measles virus infection.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References:

Measles (Rubeola) Virus Antibody, IgM and IgG (Separate Determinations), Serum

Clinical Information: The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to below 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection, but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus aids in identifying nonimmune individuals.

Useful For: Laboratory diagnosis of measles virus infection Determination of immune status of individuals to the measles virus using IgG antibody testing Documentation of previous infection with measles virus in an individual without a previous record of immunization to measles virus

Interpretation: This assay tests for both IgM and IgG-class antibodies. The presence of IgM-class antibodies, with or without the presence of IgG-class antibodies to measles virus may support a clinical
diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to
diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase
infection with measles virus. However serology may be negative for IgM-class antibodies in early
disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class
antibodies to measles should be limited to patients with clinically compatible disease. The presence
of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the
measles virus through infection or immunization. These individuals are considered immune to measles
infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune
response to immunization or no prior exposure to the measles virus. These individuals are considered
nonimmune to measles virus infection.

Reference Values:
IgM
Negative
Reference values apply to all ages.

IgG
Vaccinated: positive (≥ 1.1 AI)
Unvaccinated: negative (≤ 0.8 AI)
Reference values apply to all ages.

Clinical References:
1954;228:334-361 3. Liebert UG: Measles virus infections of the central nervous system. Intervirology
of Measles—European Region 2011;60(47):1605-1610 6. Cremer NE, Devlin VL, Riggs JL, Hagens SJ:
Anomalous antibody responses in viral infection: specific stimulation or polyclonal activation? J Clin
Microbiol 1984;20:468-472

Measles, Mumps, Rubella, and Varicella (MMRV) Immune Status
Profile, Serum

Clinical Information: The measles virus is a member of the Paramyxoviridae family of viruses,
which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and
metapneumovirus. The measles virus is among the most highly contagious infectious diseases among
unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other
respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to
12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise.
Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1) Following this
phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and
spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant
women, and those with nutritional deficiencies are particularly at risk for serious complications following
measles infection, which include pneumonia and central nervous system (CNS) involvement.(1)
Following implementation of the national measles vaccination program in 1963, the incidence of measles
infection has fallen to fewer than 0.5 cases per 1,000,000 individuals and the virus is no longer considered
endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of
nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in
2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and
the continued need for national vaccination programs.(2) The diagnosis of measles infection is often based
on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying
nonimmune individuals. Mumps: The mumps virus is a member of the Paramyxoviridae family of viruses,
which include parainfluenza virus serotypes 1-4, measles, RSV, and metapneumovirus. Mumps is highly
infectious among unvaccinated individuals and is typically transmitted through inhalation of infected
respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset
is typically acute with a prodrome of low-grade fever, headache, and malaise.(3,4) Painful enlargement of
the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in
95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women. Other complications include mumps-associated pancreatitis (<5% of cases) and CNS disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus.

However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction (PCR) in throat, saliva, or urine specimens. Rubella: Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects. The United States 2-dose measles, mumps, and rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. A total of 4 cases of rubella were reported to the Centers of Disease Control and Prevention in 2011 without any cases of congenital rubella syndrome. Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States.

Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects. The United States 2-dose measles, mumps, and rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. A total of 4 cases of rubella were reported to the Centers of Disease Control and Prevention in 2011 without any cases of congenital rubella syndrome. Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States.

Useful For: Determining immune status of individuals to measles, mumps, rubella, and varicella-zoster viruses (VZV) Documentation of previous infection with measles, mumps, rubella, or VZV in an individual without a previous record of immunization to these viruses

Interpretation: Positive measles, mumps, varicella-zoster viruses (VZV): Antibody Index (AI) value > or =1.1 Positive rubella: AI Value > or =1.0 The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies to these viruses indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to measles, mumps, rubella, or VZV are considered immune. Equivocal measles, mumps, VZV: AI value 0.9-1.0 Equivocal rubella: AI value 0.8-0.9 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative measles, mumps, VZV: AI value < or =0.8 Negative rubella: AI value < or =0.7 The absence of detectable IgG-class antibodies to measles, mumps, rubella, or VZV suggests no prior exposure to these viruses or the lack of a specific immune response to immunization.

Reference Values:
Measles, Mumps and Varicella
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages

Rubella
Vaccinated: Positive (> or =1.0 AI)
Unvaccinated: Negative (< or =0.7 AI)
Reference values apply to all ages


MARP1 607708 mecA, Molecular Detection, PCR (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MARP 607707 mecA, Molecular Detection, PCR, Varies
Clinical Information: Bacteria can acquire resistance to certain beta-lactam antibiotics through a variety of mechanisms. One such mechanism is the mecA gene. The mecA gene encodes penicillin-binding protein 2a (PBP2a), which is a PBP that has a low affinity for beta-lactam antibiotics. Bacteria expressing this gene are able to maintain cell wall synthesis even in the presence of beta-lactam antibiotics. Clinically significant mecA-mediated resistance is restricted to staphylococci. Testing of bacterial isolates by molecular methods may be needed when oxacillin or cefoxitin breakpoints are unavailable (eg, Staphylococcus species, not S aureus) or when discrepancies between cefoxitin and oxacillin phenotypic antimicrobial susceptibility testing results exist. Use of this assay may also be helpful when isolates do not grow adequately for phenotypic antimicrobial susceptibility testing (eg, staphylococcal small colony variants; SCVs).

Useful For: Detection of mecA in staphylococcal bacterial isolates Evaluation of treatment options when oxacillin or cefoxitin breakpoints are unavailable (eg, some Staphylococcus species, not S aureus) Prediction of antimicrobial resistance when bacterial growth is inadequate for phenotypic antimicrobial susceptibility testing (eg, staphylococcal small colony variants; SCVs) Assessment of discrepancies between cefoxitin and oxacillin phenotypic testing results

Interpretation: This PCR detects the mecA gene. A positive result for this mecA PCR test strongly suggests resistance to beta-lactam antibiotics other than ceftaroline in a staphylococcal isolate. If the mecA PCR test is positive, and the patient is on a beta-lactam antimicrobial that would be predicted to be resistant, the clinician should consider escalating the antimicrobial treatment to an appropriate therapy. A negative result indicates the absence of detectable DNA.

Reference Values:
Not applicable

**Reference Values:**

Initial presumptive testing by immunoassay at the following testing threshold:
Methadone: 50 ng/gm

Presumptive positive confirmed by definitive chromatography mass spectrometry (GC/MC or LC/MS-MS)

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**Clinical Information:**
Methyl-CpG-binding protein 2 (MeCP2) is a transcriptional repressor protein encoded by the MECP2 gene located on the X chromosome. Genetic mutations in MECP2 alter the expression of targeted genes and can be associated with variable phenotypes in females including classic Rett syndrome, variant or atypical Rett syndrome, mild mental retardation, and asymptomatic carriers. Males with MECP2 mutations can present with variable phenotypes as well. The variability in males can, in part, be attributed to the type of MECP2 mutation present; point mutations are typically associated with severe neonatal encephalopathy and gene duplications are associated with MECP2 duplication syndrome. Full MECP2 gene analysis via sequencing and large duplication/deletion studies has been useful in identifying germinal mutations in individuals with these clinical presentations. Rett Syndrome: Rett syndrome is an X-linked, panethnic condition with an incidence of approximately 1 in 8,500 to 1 in 15,000 females. Disease course typically begins after 6 to 18 months of apparently normal development with rapid regression in language and motor skills. A hallmark feature of this condition is repetitive, stereotyped hand movements, sometimes described as hand-wringing. Clinical criteria have been established for diagnosis of classic and atypical or variant Rett syndrome. Greater than 88% of females with a clinical diagnosis of classic Rett syndrome demonstrate a mutation by this test. The detection rate is approximately 43% for females with a clinical diagnosis of atypical or variant Rett syndrome. For individuals in whom there is clinical suspicion for Rett syndrome, but clinical criteria are not met, the detection rate is lower given the phenotypic overlap with other conditions (eg, Angelman syndrome). Nonrandom X chromosome inactivation, resulting in phenotypic variability within families, has been reported in females with MECP2 mutations. Although 99.5% of mutations associated with Rett syndrome are de novo, asymptomatic or very mildly affected carrier mothers of classically affected daughters have been reported. Genetic counseling should be provided with this, and the possibility of germline or somatic mosaicism, in mind. MECP2 Duplication Syndrome: Although MECP2 mutations are reported in males, these males typically do not present with classic Rett syndrome unless an abnormal karyotype (ie, 47,XXY) or somatic mosaicism is also present. More commonly, MECP2 mutations have been reported in karyotypically normal males presenting with neonatal encephalopathy and mental retardation syndromes. MECP2 duplication syndrome is an increasingly reported severe mental retardation syndrome characterized by infantile hypotonia, absence of speech, and progressive spasticity. Seizures and recurrent respiratory infections are commonly reported as well. These MECP2 gene duplications vary in size from 0.3 to 2.3 Mb. Although chromosome analysis can identify some larger duplications, other methods such as multiplex ligation-dependent probe amplification (MLPA) can identify essentially all MECP2 gene duplications. Males with nongene-duplication type mutations can present with other mental retardation syndromes (ie, Angelman-like syndrome) or neonatal encephalopathy and early death. To date, all males found to have an MECP2 duplication are clinically affected and have inherited the duplication from their asymptomatic mothers. Therefore, mothers of sons with MECP2 duplication syndrome are thought to be obligate carriers whose male offspring have a 50% risk of being affected.

**Useful For:** Diagnosis of Rett syndrome or other MECP2-related disorders

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MCADZ 35478**

**Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency Full Gene Analysis, Varies**

**Clinical Information:** Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an autosomal recessive inherited defect in the mitochondrial oxidation of fatty acids. The mitochondrial beta-oxidation pathway plays a major role in energy production, especially during periods of fasting and physical exertion. MCAD deficiency is prevalent among individuals of northern European origin, affecting 1 in 4,900 to 1 in 17,000 individuals, with a carrier frequency estimated as high as 1 in 40 for some populations. Phenotypic expression of MCAD deficiency is episodic in nature (ie, asymptomatic between attacks). Symptoms are typically precipitated by any stress (eg, fever, infection, vaccination) and mostly occur during the first 2 years of life, although some cases have been diagnosed in adulthood. Characteristic features of MCAD deficiency include: Reye-like syndrome (an acquired encephalopathy characterized by recurrent vomiting, agitation, and lethargy), fasting intolerance with vomiting, recurrent episodes of hypoglycemic coma, hypoketotic dicarboxylic aciduria, low plasma and tissue levels of carnitine, hepatic failure with fat infiltration (fatty liver), encephalopathy, and rapidly progressive deterioration leading to death. MCAD deficiency has also been associated with sudden infant death or sudden unexpected death syndrome. Review of clinical features and biochemical analysis via plasma acylcarnitines (ACRN / Acylcarnitines, Quantitative, Plasma), fatty acid profile (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture), urine organic acids (OAU / Organic Acids Screen, Urine), and urine acylglycines (ACYLG / Acylglycines, Quantitative, Urine) are always recommended as the initial evaluation for MCAD. If previously performed, the results of these biochemical assays should be included with the specimen as they are necessary for accurate interpretation of the MCAD sequence analysis. The MCAD gene (ACADM) maps to 1p31 and has 12 exons, spanning 44 kb of DNA. Most mutations are family-specific with the exception of the recurrent A->G transition at nucleotide 985 (985A->G). Among MCAD-deficient patients, approximately 52% are homozygous for the 985A->G mutation. The majority of the remaining patients are compound heterozygous for the 985A->G mutation and a different mutation.

**Useful For:** Confirmation of diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (as a follow-up to biochemical analyses) Screening of at-risk carriers of MCAD deficiency when an affected relative has not had molecular testing Diagnosis of MCAD deficiency in autopsy specimens

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

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**Current as of June 14, 2021 12:13 pm CDT**

800-533-1710 or 507-266-5700 or mayocliniclabs.com

Page 1654
MEGR

82347

Megrim, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to megrim Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<thead>
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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


MELAI

as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1655
Melaleuca leucadendron, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Melaleuca leucadendron. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: responsible for allergic disease and/or anaphylactic episode. To confirm sensitization prior to beginning immunotherapy. To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tbody>
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<td>0</td>
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<td>1</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Melan A (MART-1) Immunostain, Technical Component Only

Clinical Information: Melanoma antigen recognized by T cells or Melan-A (MART-1), is a protein with unknown function that is associated with endoplasmic reticulum and melanosomes. Melan A is a sensitive and specific marker for the diagnosis of melanoma. Melan A is also found in other tumors of melanocytic origin such as clear cell sarcoma, melanotic neurofibroma, melanotic schwannoma, as well as in perivascular epithelioid cell tumor. The monoclonal antibody A103 for Melan A cross-reacts with steroid hormone producing cells and tumors. Consequently, adrenocortical adenomas/carcinomas and sex cord-stromal tumors of the ovary and testis may exhibit staining.

Useful For: Aids in the identification of melanoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a
pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FMARP 75449
Melanoma Associated Retinopathy MAR Panel by Immunoblot and IHC

Reference Values: A final report will be provided.

MELP 35343
Melanoma Targeted Gene Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the following genes known to be associated with melanoma: BRAF, GNA11, GNAQ, KIT, and NRAS. This includes the common BRAF V600E and V600K mutations. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with melanoma. See Targeted Gene Regions Interrogated by Melanoma Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

Useful For: Diagnosis and management of patients with melanoma Simultaneously interrogating multiple gene targets including BRAF (e.g., V600E and V600K); GNAQ, GNA11, KIT and NRAS

Interpretation: An interpretive report will be provided.

Reference Values: An interpretative report will be provided.


**FMELA 75386**

**Melatonin, Plasma**

**Interpretation:** Endogenous concentrations of melatonin are of the order of less than 0.02-0.2 ng/mL and vary based on time of day and age. An oral use of a 6 mg dose in 60 female subjects produced an average peak concentration of 12 ng/mL with a peak time of approximately 0.75 hours. A 10 mg dose in male subjects produced an average concentration of 9.8 ng/mL. Melatonin's major side effect profile includes drowsiness and sleepiness.

**Reference Values:**

Reporting limit determined each analysis.

Units: ng/mL

**FMELG 57652**

**Melons IgG**

**Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**MELN 82762**

**Melons, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to melons Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Meningitis/Encephalitis Pathogen Panel, PCR, Spinal Fluid**

**Clinical Information:** Bacteria: Escherichia coli K1 strains account for nearly 80% of E coli isolated from cerebrospinal fluid (CSF). While most E coli are harmless enteric organisms residing in the intestines of humans and animals, some cause gastrointestinal illness and extraintestinal infections (eg, urinary tract infections, bacteremia, and meningitis). E coli associated with meningitis contain virulence factors that contribute to their pathogenesis by allowing them to spread through the blood, hijack normal host cell functions, infiltrate endothelial cells, and gain access to the tissues of the central nervous system (CNS). The K1 antigen is a capsule that protects the bacteria from the immune system. These infections are of particular concern for preterm babies and neonates, and are responsible for nearly 45% and 30% of meningitis cases in these age groups with a mortality rate of 13% and 25%, respectively. Infections in adults are less common and generally opportunistic in nature following exposure of sterile organs to contents of the gastrointestinal tract following trauma or surgical procedures; the mortality rate for adults is reported to be 28% to 36%. Haemophilus influenzae is a Gram-negative coccobacillus that is isolated exclusively from humans. Strains of H influenzae are divided into 2 groups based on the presence or absence of a polysaccharide capsule. Encapsulated strains are further divided into 6 serotypes (a through f). Prior to widespread use of the H influenzae type b (Hib) conjugate vaccines, Hib caused more than 80% of invasive H influenzae infections, predominantly in children under the age of 5, with a mortality rate of 3% to 6% and a further 20% to 30% developing permanent sequelae ranging from mild hearing loss to mental retardation. In areas with routine vaccination, the majority of invasive H influenzae infections are caused by nontypeable strains and remain an important cause of meningitis, particularly for persons with predisposing conditions such as otitis or sinusitis, diabetes, immune deficiency, or head trauma with CSF leakage. Meningitis due to
H influenzae occurs at an estimated rate of 0.08 cases per 100,000 in the United States, and it has been reported as the etiologic agent of bacterial meningitis in 20% to 50% of cases worldwide over the last several decades. Listeria monocytogenes, the causative agent of listeriosis, is a Gram-positive bacillus that is ubiquitous in soil and water and can be found in the gastrointestinal tract of up to 5% of healthy human adults. Listeriosis is considered one of the most severe bacterial foodborne infections due to its high mortality rate even with early antibiotic treatment (11%-60%). Invasive listeriosis can result in abortion, sepsis, meningitis, and meningoencephalitis. Populations at risk for developing invasive listeriosis include the immunosuppressed, pregnant women, neonates, fetuses, and the elderly.

Meningitis due to L monocytogenes is reported to be approximately 0.05 cases per 100,000 persons in the United States per year, and causes from 0.5% to 2.0% of bacterial meningitis cases in non-US countries. Neisseria meningitidis (encapsulated) is a fastidious, aerobic, Gram-negative diplococcus that is transmitted by contact with mucus or respiratory droplets, often from asymptomatic carriers. There are at least 12 different serogroups of N meningitidis, 6 of which are associated with epidemics (groups A, B, C, W135, X, and Y). The serogroup refers to types of capsular antigens, generally only encapsulated N meningitidis are considered pathogenic. Meningococcal disease (meningitis and meningococcemia) is rare in developed countries, but can occur in outbreaks and is still a public health issue in developing countries. It is most common in infants, children, and young adults, and appears in places with crowded living conditions (eg, college dormitories and military barracks). Seasonal incidence peaks in late winter and early spring with an annual incidence of about 0.2 cases per 100,000 in the United States. The disease can progress extremely quickly (<24 hours) with hypotension, multiorgan dysfunction, shock, peripheral ischemia, and limb loss, and has a mortality rate of approximately 5% to 10%. There are licensed meningococcal vaccines available in United States that may be used in persons of all ages, depending on the vaccine. Despite extensive vaccination efforts worldwide, several serogroups of N meningitidis still cause seasonal outbreaks, particularly in sub-Saharan Africa. Extreme reductions in serogroup C meningococcal meningitis have been observed in countries where vaccines providing protection for this serogroup have been introduced. Streptococcus agalactiae (group B Streptococcus or GBS) is an important cause of meningitis in neonates, particularly those that are preterm, and is often coincident with neonatal sepsis. The most important risk factor for neonatal disease is maternal colonization with GBS. Since 1996, the CDC guidelines (updated in 2010) have called for prophylactic antibiotic treatment several hours before delivery in at-risk deliveries, resulting in declining rates of neonatal GBS. In adult patients, GBS is associated with advanced age or severe underlying health conditions. Overall incidence in the United States is estimated to be 0.25 infections per 100,000 and neonatal GBS disease has ranged from 0.2 to 2.4 per 1,000 births in Europe over the last few decades. Mortality rates range from 10% for neonates to 25% to 30% in adults. Streptococcus pneumoniae colonizes the upper respiratory tract, and is the most frequently isolated respiratory pathogen in community-acquired pneumonia. It is also a major cause of meningitis, particularly in pediatric and elderly patients, and especially in those with underlying medical conditions, with an incidence rate of approximately 0.8 infections per 100,000 in the United States, and causes 20% to 31% of bacterial meningitis cases in non-US countries. The mortality rate is also high: 8% to 15% for children and 20% to 37% for adults. Mortality approaches 50% in resource-poor countries, especially where HIV coinfection is a factor. Neurological sequelae (cognitive impairment, deafness, epilepsy) are reported in up to 40% of survivors. Vaccines have helped reduce the risk of both invasive disease and pneumococcal pneumonia by 50% to 80%. Viruses: Human cytomegalovirus (CMV) is a double-stranded DNA virus of the Herpesviridae family. Seroprevalence data show that infection is nearly ubiquitous in the population worldwide, with rates approaching 100% in developing countries and 36% to 90% in the United States depending on age and race/ethnicity. While severe illness in immunocompetent patients is rare, CMV is an opportunistic pathogen in immunocompromised or immunosuppressed individuals, either as an initial infection or activation of a latent infection. In some patients (eg, transplant recipients), CMV may infect the central nervous system and cause meningoencephalitis. Enteroviruses (EV) are small RNA viruses that are members of the Picornaviridae family and are associated with human illnesses ranging from asymptomatic or mild infections to serious CNS illnesses requiring hospitalization. Infection rates are highest in children, with the majority of infections occurring during summer months. The most common EV serotypes are coxsackie viruses A9 and B1, and echoviruses 6, 9, and 18, which account for over 50% of serotyped detections. Infections are spread via fecal-oral and respiratory routes and can spread quickly in community settings, particularly in areas with poor sanitation. EV is one of the commonly identified causes of infectious encephalitis/meningitis, with prevalence rates reported between 5.5% and 30% depending on location and patient demographics. Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are DNA viruses of the
Herpesviridae family named for the spreading skin ulcerations caused by infection with these viruses. HSV-1 infections usually occur early in childhood and manifest primarily as oral lesions, whereas HSV-2 is primarily associated with genital lesions and infections are acquired later in life and are associated with sexual activity. HSV establishes residency in nerve cells following initial infection (which is asymptomatic in most cases). Viral activation resulting in lesions or other severe disease outcomes (such as CNS infection), may occur throughout life, and are associated with fever, injury, exposure to ultraviolet irradiation (sunlight), emotional stress, hormone irregularities, and changes in immune status. In the United States, overall seroprevalence for HSV-1 is around 60%. The overall seroprevalence for HSV-2 is around 16%, but varies with age, sex, and ethnicity. Worldwide, it is estimated that approximately 90% of people are infected with HSV-1; HSV-2 is less common with 15% to 80% of people infected. HSV is one of the most common causes of viral encephalitis and is a significant cause of meningitis. In a large study of over 1,600 CSF specimens in the United Kingdom, HSV-1 was found in 25 (1.5%) patients (almost all of whom had encephalitis) and HSV-2 was found in 33 (1.9%) patients (almost all of whom had meningitis). This overall prevalence of approximately 3% in CSF is similar to that seen in a recent study of CSF patients in New York State. This study also saw a similar distribution of HSV-1 and HSV-2 in encephalitis versus meningitis. Human herpesvirus 6 (HHV-6) was discovered in the mid-1980s, when the rise of immunocompromised patients led to an increase in the population susceptible to severe disease outcome. There are 2 species: HHV-6A and HHV-6B. Studies have shown that over 95% of persons over the age of 2 are positive for 1 or both variants and the infection establishes latency due to viral integration into host cells. While primary infection with HHV-6B causes roseola in infants, the clinical manifestations of primary infection with HHV-6A remain somewhat undefined; however, some studies have suggested that HHV-6A infection may be linked to inflammatory or neurological disease, and that HHV-6A may have an increased neurotropism compared to HHV-6B. This hypothesis is supported by the finding that HHV-6 inhabits CNS tissues, including the brain, where it may cause tissue damage leading to encephalitis or meningitis. Furthermore, HHV-6 was identified in CSF of 1.8% of patients with encephalitis or meningitis in a recent study. CNS disease associated with HHV-6 is found in both children and adults, suggesting CNS invasion during primary infection is possible. While immunocompetent patients may experience CNS infection, it is much more common in severely immunosuppressed individuals. However, HHV-6 is known to reactivate in asymptomatic patients and can be detected by PCR in otherwise healthy individuals without signs of active HHV-6 infection. Studies of HHV-6 in normal brain tissue have also identified HHV-6 DNA via PCR in up to 85% of patients without signs of active infection and HHV-6 DNA may persist in the CSF after acute infection. In a study of 56 allogeneic stem cell transplant patients, HHV-6 DNA was detected in the CSF of 14 (27%) patients without CNS symptoms. Given the prevalence of latent infection and potential for asymptomatic reactivation, positive HHV-6 results should be carefully interpreted in association with clinical symptoms and supplemental laboratory testing. Human parechoviruses (HPeV) comprise another genus of the Picornaviridae family. HPeV were originally classified as enterovirus upon their discovery in the 1950s and at least a dozen serotypes have been identified. Seroprevalence for HPeV-1 approaches 100% in adult populations, with most infections occurring during early childhood. As with EV, infections are spread via fecal-oral and respiratory routes; with the most common symptoms being mild respiratory or gastrointestinal illness. CNS disease from HPeV-1 is rare, but HPeV-3 is associated with severe disease outcomes such as sepsis, encephalitis, meningitis, and hepatitis in children younger than 3 months of age. Recent studies of CSF from infants with suspected CNS illness or sepsis have demonstrated HPeV at a prevalence of 3% to 17%, nearly all of which were HPeV-3. Magnetic resonance imaging studies of infants who survive HPeV CNS disease show damage to the white matter of the brain and developmental disabilities later in life. Varicella zoster virus (VZV) is a double-stranded DNA virus of the Herpesviridae family that usually causes infections in childhood (chicken pox) and establishes latent presence in cells that can reactivate later in life (zoster or shingles). VZV is primarily spread through respiratory secretions or direct contact with lesions of an infected individual, and infection of new hosts begins within the epithelial cells of the respiratory tract. Following primary infection (fever and malaise accompanied with a maculopapular rash), VZV establishes itself in the sensory ganglia of the nervous system where it remains latent. In the United States, nearly 90% of the population had been infected with VZV before the advent of vaccines. Similar rates have been reported in European countries. Of those infected, between 10% and 30% develop zoster (a painful rash along the dorsal ganglia), primarily later in life. It is estimated that the median global incidence of zoster is 4.0 to 4.5 per 1,000 person-years, which highlights the frequency of VZV reactivation worldwide. Studies have shown that VZV is transiently detectable by PCR in the blood of older, asymptomatic individuals (both immunocompetent and
immunocompromised), suggesting reactivation occurs throughout life but is usually managed by the immune system. Encephalitis and meningitis are complications of both varicella and zoster infections. In 1 study, VZV was the third most detected virus among patients with signs and symptoms of encephalitis or meningitis, with a reported prevalence of 1.9% in the study population. There are live, attenuated VZV vaccines licensed for use in the United States for the vaccination of children against varicella and adults against zoster. Yeast: Cryptococcus neoformans and Cryptococcus gattii are pathogenic fungi that are acquired by inhalation and can spread to other organ systems (particularly the brain and meninges). C neoformans is considered an opportunistic pathogen of immunocompromised individuals. It is the AIDS-defining illness in up to 50% of AIDS patients. C gattii infections are relatively rare but appear to be increasing. While typically associated with tropical and subtropical climates, since the 1990s, C gattii infections have been reported in British Columbia, Canada, the US Pacific Northwest region, the Northeastern US, and in Europe. In addition to those with reduced immune function, C gattii can also cause disease in the immunocompetent, particularly in persons with underlying health conditions. Mortality from cryptococcal meningitis is high, ranging from 10% to nearly 50% in immunocompromised patients.(1)

**Useful For:** Rapid detection of meningitis and encephalitis caused by: - Escherichia coli K1 (K1 serotype only) - Haemophilus influenzae - Listeria monocytogenes - Neisseria meningitidis (encapsulated strains only) - Streptococcus agalactiae (Group B Strept) - Streptococcus pneumoniae - Cytomegalovirus (CMV) - Enterovirus - Herpes simplex virus 1 (HSV-1) - Herpes simplex virus 2 (HSV-2) - Herpes simplex virus 6 (HHV-6) - Human parechovirus - Varicella zoster virus (VZV) - Cryptococcus neoformans/gattii

This test is not intended for use with CSF collected from indwelling medical devices (eg, CSF shunts). This test is not recommended as a test of cure.

**Interpretation:** A positive result for 1 or more of the organisms suggests that nucleic acid from the organism was present in the sample. A negative result suggests that the nucleic acid of 14 common pathogens of the central nervous system was not present in the sample. A negative result should not rule-out central nervous system (CNS) infection in patients with a high pretest probability for meningitis or encephalitis. The assay does not test for all potential infectious agents of CNS disease. Negative results should be considered in the context of a patient's clinical course and treatment history, if applicable.

False-negative results may occur when the concentration of nucleic acid in the specimen is below the limit of detection for the test. Detection of multiple viruses or bacteria or viruses and bacteria may be observed with this test. In these situations, the clinical history and presentation should be reviewed thoroughly to determine the clinical significance of multiple pathogens in the same specimen. Results are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings.

**Reference Values:**
Negative (for all targets)

**Clinical References:**
**Mephedrone, MDPV and Methylone, Urine**

**Reference Values:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Units</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mephedrone</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>MDPV</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Methylone</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Qualitative analysis for Mephedrone, Methyleneoxyprovalerone (MDPV) and Methylone
Screening threshold: 1.0 ng/mL

**Mephobarbital and Phenobarbital, Serum**

**Clinical Information:** Mephobarbital is an orally administered, methylated barbiturate used for the treatment of epilepsy.(1,2) It is demethylated by hepatic microsomal enzymes to generate its major metabolite, phenobarbital. During long-term use, most of the mephobarbital activity can be attributed to the accumulation of phenobarbital. Consequently, the pharmacological properties, toxicity, and clinical uses of mephobarbital are the same as phenobarbital.(1,2) The use of mephobarbital is uncommon as it offers no significant advantage over phenobarbital alone.(1,2)

**Useful For:** Monitoring of mephobarbital and phenobarbital therapy

**Interpretation:** Mephobarbital concentrations above 15 mcg/mL have been associated with toxicity. Phenobarbital concentrations between 35 and 80 mcg/mL have been associated with slowness, ataxia, and nystagmus, while concentrations above 100 mcg/mL have been associated with coma without reflexes.

**Reference Values:**

- **MEPHOBARBITAL**
  - Therapeutic range: 1.0-7.0 mcg/mL
  - Toxic concentration: > or =15.0 mcg/mL

- **PHENOBARBITAL**
  - Therapeutic range
    - Children: 15.0-30.0 mcg/mL
    - Adults: 20.0-40.0 mcg/mL
  - Toxic concentration: > or =60.0 mcg/mL

**Clinical References:**


**Mercaptopurine (6-MP, Purinethol)**

**Reference Values:**

- **Units:** ng/mL

**Current as of June 14, 2021 12:13 pm CDT**
Mercaptopurine may be administered as an antineoplastic or may be present as a metabolite of the immunosuppressant drug azathioprine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses of either mercaptopurine or azathioprine produce 6-mercaptopurine serum concentrations of less than 1000 ng/mL.

**Mercury Occupational Exposure, Random, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For more information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity due to occupational exposure in random urine specimens

**Reference Values:**
Only orderable as part of a profile. For more information see:
- HGUOE / Mercury Occupational Exposure, Random, Urine
- HMUOE / Heavy Metal Occupational Exposure, with Reflex, Random, Urine

**Clinical References:**

**Mercury Occupational Exposure, Random, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. It had always been thought that urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) For additional information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity due to occupational exposure

**Interpretation:** Daily urine excretion of mercury greater than 50 mcg/day indicates significant exposure (per World Health Organization standard).

**Reference Values:**
Biological Exposure Index (BEI): <35 mcg/g creatinine prior to shift

**Clinical References:**
Mercury, 24 Hour, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. It had always been thought that urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) For additional information, see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity in 24-hour urine specimens

Interpretation: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:
0-17 years: not established
> or =18 years: <2 mcg/24 hour
Toxic concentration: >50 mcg/24 hour

The concentration at which toxicity is expressed is widely variable between patients. 50 mcg/24 hour is the lowest concentration at which toxicity is usually apparent.


Mercury, Blood

Clinical Information: Mercury (Hg) is essentially nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(2+), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg ([CH3Hg][+]), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Â Not Toxic - Hg(0) < Hg(2+) << [CH3Hg](+) -- Very Toxic Â Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents such as chlorine. Hg(0) can be bioconverted to both Hg(+2) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(2+), [CH3Hg](+), and (CH3)(2+)Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(2+) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein-a stereoisomeric change-with subsequent loss of the unique activity associated with that protein. Because Hg(2+) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as [CH3Hg](+), are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can
cause release of mercury from dental amalgams greatly above normal. The normal bacterial flora present in the mouth converts a fraction of this to Hg(2+) and [CH3Hg](+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain less than 0.3 mcg/g of mercury, but some game fish contain more than 2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is below 50 mcg/day.

**Useful For:** Detecting mercury toxicity

**Interpretation:** The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually below 10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is above 50 ng/mL if exposure is due to alkyl Hg, or above 200 ng/mL if exposure is due to Hg(2+).

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;10 ng/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**


**HGHAR 8498**

**Mercury, Hair**

**Clinical Information:** Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If the hair can be segregated by length, such an exercise may be useful in identifying the time of exposure.

**Useful For:** Detecting mercury exposure in hair specimens

**Interpretation:** Normally, hair contains less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury may have occurred.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15 years</td>
<td>not established</td>
</tr>
<tr>
<td>&gt; or =16 years</td>
<td>&lt;1.0 mcg/g of hair</td>
</tr>
</tbody>
</table>

**Clinical References:**


**HGNA 89856**

**Mercury, Nails**

**Clinical Information:** Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms.
If the nails can be segregated by length, such an exercise may be useful in identifying the time of exposure.

**Useful For:** Detecting mercury exposure

**Interpretation:** Normally, nails contain less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury may have occurred.

**Reference Values:**
- 0-15 years: not established
- > or =16 years: <1.0 mcg/g of nails

**Clinical References:**

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**HGRC 48546**

**Mercury/Creatinine Ratio, Random, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity in random urine specimens

**Interpretation:** Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

**Reference Values:**
Only orderable as part of profile. See HGRCR / Mercury/Creatinine Ratio, Random, Urine or HMCRU / Heavy Metal/Creatinine Ratio, with Reflex, Urine.

**Clinical References:**

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**HGCU 608903**

**Mercury/Creatinine Ratio, Random, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. It had always been thought that urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2). For additional information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity using random urine specimens

**Interpretation:** Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

**Reference Values:**
Only orderable as part of profile. For more information see:
- HGU CR / Mercury/Creatinine Ratio, Random, Urine
- HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random Urine.

HGUCR
608907

Mercury/Creatinine Ratio, Random, Urine
Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. It had always been thought that urine was a more appropriate marker of inorganic mercury, because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%), which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood. For additional information, see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity, a toxic heavy metal, using random urine specimens

Interpretation: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:
0-17 years: not established
> or =18 years: <2 mcg/g creatinine


MERKC
71538

Merkel CC (MCPyV) Immunostain, Technical Component Only
Clinical Information: Merkel cell polyomavirus (MCPyV) infections are common and typically benign. In rare instances, these infections lead to neoplastic transformations known as Merkel cell carcinoma (MCC) through the expression (nuclear) of MCPyV large T-antigen. MCPyV-positive MCC have been reported to behave less aggressively than MCPyV-negative MCC.

Useful For: Identification of Merkel cell polyomavirus (MCPyV) infected cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the...
context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Mesoridazine (Serentil)**

**Reference Values:**
Reference Range: 150 - 1000 ng/mL

**Mesothelial Cell (HBME-1) Immunostain, Technical Component Only**

**Clinical Information:** This mesothelial cell (HBME-1) antibody stains an unknown antigen in the microvillous processes of mesothelial cells with a “thick membrane” staining pattern. The antibody also reacts with a wide variety of normal and neoplastic tissues. This stain is diagnostically useful in distinguishing thyroid carcinoma (papillary and follicular types) from thyroid follicular adenomas, which usually lack staining.

**Useful For:** Classification of thyroid carcinomas

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
N/A

**Clinical References:**

**Mesquite, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to mesquite Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


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**METF**

**MET (7q31), FISH, Tissue**

**Clinical Information:** MET is a proto-oncogene and its overexpression is associated with disease progression. Recent studies have shown MET amplification to be a major mechanism of acquired resistance to epidermal growth factor receptor tyrosine kinase domain inhibitor (EGFR-TKI). MET amplification has been reported in approximately 5% of patients not treated with EGFR-TKI and up to 20% of patients with acquired resistance to gefitinib or erlotinib.

**Useful For:** Providing prognostic information and guiding treatment primarily for patients with lung, gastric, and renal tumors as well as other tumor types

**Interpretation:** A positive result is detected when the MET:D7Z1 ratio is > or =2.0. The MET locus is reported as amplified when the MET:D7Z1 ratio of 2.0 or greater. Patients with 5 or more copies of MET have a poor prognosis. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:** An interpretive report will be provided.


Metamycoplasma hominis, Molecular Detection, PCR, Blood

Clinical Information: Metamycoplasma hominis, previously Mycoplasma hominis, has been associated with a number of clinically significant infections, although it is also part of the normal genital flora. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may occur without specific treatment, in premature infants clinical manifestations of meningoencephalitis have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of M hominis infection in lung transplant recipients.

Useful For: Rapid, sensitive, and specific identification of Metamycoplasma hominis from whole blood

Interpretation: A positive PCR result for the presence of a specific sequence found within the Metamycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but does not rule-out infection as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection, and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of M hominis infection in lung transplant recipients. Polymerase chain reaction (PCR) detection of M hominis is sensitive, specific, and provides same-day results. Although this organism can occasionally be detected in routine plate cultures, this is neither a rapid nor a sensitive approach to detection. Specialized cultures are more time consuming than the described PCR assay. The described PCR assay has replaced conventional culture for M hominis at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

**Useful For:** Rapid, sensitive, and specific identification of Metamycoplasma hominis from synovial fluid, genitourinary, reproductive, lower respiratory sources, pleural/chest fluid, pericardial fluid, and wound specimens This test is not intended for medicolegal use.

**Interpretation:** A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Metamycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but does not rule-out infection as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

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**META3 65158 Metanephrines with 3-Methoxytyramine, 24 Hour, Urine**

**Clinical Information:** Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating (“spells”). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Dopamine secreting tumors are rarer than norepinephrine and epinephrine secreting tumors. 3-Methoxytyramine (3MT), metanephrine, and normetanephrine are the metabolites of dopamine, epinephrine, and norepinephrine, respectively. These metabolites are further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. In patients that are highly suspect for pheochromocytoma, it may be best to screen by measuring plasma free fractionated metanephrines (a more sensitive assay). This test may be used as the first test for low-suspicion cases and also as a confirmatory study in patients with a less than 2-fold elevation in plasma free fractionated metanephrines or catecholamines. This is highly desirable, as the very low population incidence rate of pheochromocytoma (<1:100,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures. Complete 24-hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a “spell.”

**Useful For:** A first- and second-tier screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas Testing in conjunction with or as an alternative to plasma metanephrine or catecholamine testing.
**Interpretation:** Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Increased 3-methoxytyramine (3MT) levels are found in patients with pheochromocytoma and dopamine-secreting tumors. Total urine metanephrine levels of 1300 mcg/24 hours and less, and 3MT levels of 306 mcg/24 hours or less in males and 242 mcg/24 hours or less in females, can be detected in non-pheochromocytoma hypertensive patients. Further clinical investigation (eg, radiographic studies) is warranted in patients whose total urinary metanephrine levels are above 1300 mcg/24 hours (approximately 2 times the upper limit of normal) or whose 3MT levels are elevated and there is a very high clinical index of suspicion. For patients with total urinary metanephrine levels below 1300 mcg/24 hours, further investigations may also be indicated if either the normetanephrine or the metanephrine fraction of the total metanephrines exceeds their respective upper limit for hypertensive patients. Finally, repeat testing or further investigations may occasionally be indicated in patients with urinary metanephrine levels below the hypertensive cutoff, or even normal levels, if there is a very high clinical index of suspicion.

**Reference Values:**

3-Methoxytyramine:
- Males: < or =306 mcg/24 hours
- Females: < or =242 mcg/24 hours

**METANEPHRINE**

**Males**
- Normotensives
  - 3-8 years: 29-92 mcg/24 hours
  - 9-12 years: 59-188 mcg/24 hours
  - 13-17 years: 69-221 mcg/24 hours
  - ≥ or =18 years: 44-261 mcg/24 hours
- Reference values have not been established for patients that are <36 months of age.
- Hypertensives: <400 mcg/24 hours

**Females**
- Normotensives
  - 3-8 years: 18-144 mcg/24 hours
  - 9-12 years: 43-122 mcg/24 hours
  - 13-17 years: 33-185 mcg/24 hours
  - ≥ or =18 years: 30-180 mcg/24 hours
- Reference values have not been established for patients that are <36 months of age.
- Hypertensives: <400 mcg/24 hours

**NORMETANEPHRINE**

**Males**
- Normotensives
  - 3-8 years: 34-169 mcg/24 hours
  - 9-12 years: 84-422 mcg/24 hours
  - 13-17 years: 91-456 mcg/24 hours
  - 18-29 years: 103-390 mcg/24 hours
  - 30-39 years: 111-419 mcg/24 hours
  - 40-49 years: 119-451 mcg/24 hours
  - 50-59 years: 128-484 mcg/24 hours
  - 60-69 years: 138-521 mcg/24 hours
  - ≥ or =70 years: 148-560 mcg/24 hours
- Reference values have not been established for patients that are <36 months of age.
- Hypertensives: <900 mcg/24 hours

**Females**
- Normotensives
  - 3-8 years: 29-145 mcg/24 hours
  - 9-12 years: 55-277 mcg/24 hours
13-17 years: 57-286 mcg/24 hours
18-29 years: 103-390 mcg/24 hours
30-39 years: 111-419 mcg/24 hours
40-49 years: 119-451 mcg/24 hours
50-59 years: 128-484 mcg/24 hours
60-69 years: 138-521 mcg/24 hours
> or =70 years: 148-560 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.
Hypertensives: <900 mcg/24 hours

TOTAL METANEPHRINE
Males
Normotensives
3-8 years: 47-223 mcg/24 hours
9-12 years: 201-528 mcg/24 hours
13-17 years: 120-603 mcg/24 hours
18-29 years: 190-583 mcg/24 hours
30-39 years: 200-614 mcg/24 hours
40-49 years: 211-646 mcg/24 hours
50-59 years: 222-680 mcg/24 hours
60-69 years: 233-716 mcg/24 hours
> or =70 years: 246-753 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.
Hypertensives: <1300 mcg/24 hours

Females
Normotensives
3-8 years: 57-210 mcg/24 hours
9-12 years: 107-394 mcg/24 hours
13-17 years: 113-414 mcg/24 hours
18-29 years: 113-414 mcg/24 hours
30-39 years: 149-535 mcg/24 hours
40-49 years: 156-561 mcg/24 hours
50-59 years: 164-588 mcg/24 hours
60-69 years: 171-616 mcg/24 hours
> or =70 years: 180-646 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.
Hypertensives: <1300 mcg/24 hours

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Metanephrines, Fractionated, 24 Hour, Urine

Clinical Information: Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating (spells). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethyle catecholamines into metanephrines that are secreted into circulation. In patients that are highly suspect for pheochromocytoma, it may be best to screen by measuring plasma free fractionated metanephrines (a more sensitive assay). The 24-hour urinary fractionated metanephrines (a more specific assay) may be used as the first test for low suspicion cases and also as a confirmatory study in patients with a less than 2-fold elevation in plasma free fractionated metanephrines. This is highly desirable, as the very low population incidence rate of pheochromocytoma (<1:100,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures. Complete 24-hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a spell.

Useful For: A first- and second-order screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas Confirming positive plasma metanephrine results

Interpretation: Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Total urine metanephrines 1300 mcg/24 hours and lower can be detected in nonpheochromocytoma hypertensive patients. Further clinical investigation (eg, radiographic studies) is warranted in patients whose total urinary metanephrine levels are above 1300 mcg/24 hours (approximately 2 times the upper limit of normal). For patients with total urinary metanephrine levels below 1300 mcg/24 hours, further investigations may also be indicated if either the normetanephrine or the metanephrine fraction of the total metanephrines exceed their respective upper limit for hypertensive patients. Finally, repeat testing or further investigations may occasionally be indicated in patients with urinary metanephrine levels below the hypertensive cutoff, or even normal levels, if there is a very high clinical index of suspicion.

Reference Values:

METANEPHRINE
Males
Normotensives
3-8 years: 29-92 mcg/24 hours
9-12 years: 59-188 mcg/24 hours
13-17 years: 69-221 mcg/24 hours
> or =18 years: 44-261 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.
Hypertensives: <400 mcg/24 hours
Females
Normotensives
3-8 years: 18-144 mcg/24 hours
9-12 years: 43-122 mcg/24 hours
13-17 years: 33-185 mcg/24 hours
> or =18 years: 30-180 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.
Hypertensives: <400 mcg/24 hours

NORMETANEPHRINE
Males
Normotensives
3-8 years: 34-169 mcg/24 hours
9-12 years: 84-422 mcg/24 hours
13-17 years: 91-456 mcg/24 hours
18-29 years: 103-390 mcg/24 hours
30-39 years: 111-419 mcg/24 hours
40-49 years: 119-451 mcg/24 hours
50-59 years: 128-484 mcg/24 hours
60-69 years: 138-521 mcg/24 hours
> or =70 years: 148-560 mcg/24 hours

Reference values have not been established for patients that are <36 months of age.

Hypertensives: <900 mcg/24 hours
Females

Normotensives
3-8 years: 29-145 mcg/24 hours
9-12 years: 55-277 mcg/24 hours
13-17 years: 57-286 mcg/24 hours
18-29 years: 103-390 mcg/24 hours
30-39 years: 111-419 mcg/24 hours
40-49 years: 119-451 mcg/24 hours
50-59 years: 128-484 mcg/24 hours
60-69 years: 138-521 mcg/24 hours
> or =70 years: 148-560 mcg/24 hours

Reference values have not been established for patients that are <36 months of age.

Hypertensives: <900 mcg/24 hours

TOTAL METANEPHRINE
Males
Normotensives
3-8 years: 47-223 mcg/24 hours
9-12 years: 201-528 mcg/24 hours
13-17 years: 120-603 mcg/24 hours
18-29 years: 190-583 mcg/24 hours
30-39 years: 200-614 mcg/24 hours
40-49 years: 211-646 mcg/24 hours
50-59 years: 222-680 mcg/24 hours
60-69 years: 233-716 mcg/24 hours
> or =70 years: 246-753 mcg/24 hours

Reference values have not been established for patients that are <36 months of age.

Hypertensives: <1,300 mcg/24 hours
Females

Normotensives
3-8 years: 57-210 mcg/24 hours
9-12 years: 107-394 mcg/24 hours
13-17 years: 113-414 mcg/24 hours
18-29 years: 142-510 mcg/24 hours
30-39 years: 149-535 mcg/24 hours
40-49 years: 156-561 mcg/24 hours
50-59 years: 164-588 mcg/24 hours
60-69 years: 171-616 mcg/24 hours
> or =70 years: 180-646 mcg/24 hours

Reference values have not been established for patients that are <36 months of age.

Hypertensives: <1,300 mcg/24 hours

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

**Clinical References:**
2. Pacak K, Linehan WM, Eisenhofer G, et al: Recent advances in genetics,
Sawka AM, Singh RJ, Young WF Jr: False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. Endocrinologist 2001;11:421-423

PMET
81609

**Metanephrines, Fractionated, Free, Plasma**

**Clinical Information:** Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine (collectively referred to as metanephrines) are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. The metanephrines are stable metabolites and are cosecreted directly with catecholamines by pheochromocytomas and other neural crest tumors. This results in sustained elevations in plasma free metanephrine levels, making them more sensitive and specific than plasma catecholamines in the identification of pheochromocytoma patients.(1) Metanephrine and normetanephrine are both further metabolized to conjugated metanephrines and vanillylmandelic acid.

**Useful For:** Screening test for presumptive diagnosis of catecholamine-secreting pheochromocytomas or paragangliomas

**Interpretation:** In the normal population, plasma metanephrine and normetanephrine levels are low, but in patients with pheochromocytoma or paragangliomas, the concentrations may be significantly elevated. This is due to the relatively long half-life of these compounds, ongoing secretion by the tumors and, to a lesser degree, peripheral conversion of tumor-secreted catecholamines into metanephrines. Measurement of plasma free metanephrines appears to be the best test for excluding pheochromocytoma. The test's sensitivity approaches 100%, making it extremely unlikely that individuals with normal plasma metanephrine and normetanephrine levels suffer from pheochromocytoma or paraganglioma.(1,2) Due to the low prevalence of pheochromocytomas and related tumors (<1:100,000), it is recommended to confirm elevated plasma free metanephrines with a second, different testing strategy in order to avoid large numbers of false-positive test results.(3) The recommended second-line test is measurement of fractionated 24-hour urinary metanephrines (METAFL Metanephrines, Fractionated, 24 Hour, Urine). In most cases this strategy will suffice in confirming or excluding the diagnosis. Occasionally, it will be necessary to extend this approach if there is a very high clinical index of suspicion or if test results are nonconclusive. In these cases, repeat plasma and urinary metanephrines testing, additional measurement of plasma or urinary catecholamines, or imaging procedures might be indicated. Elevated results are reported with appropriate comments.

**Reference Values:**
- METANEPHRINE, FREE  
  <0.50 nmol/L
- NORMETANEPHRINE, FREE  
  <0.90 nmol/L


Metanephrines, Fractionated, Random, Urine

Clinical Information: Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine and norepinephrine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. While screening for pheochromocytoma is best accomplished by measuring plasma free fractionated metanephrines (a more sensitive assay), follow-up testing with urinary fractionated metanephrines (a more specific assay) may identify false-positives. Twenty-four hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."

Useful For: A second-order screening test for the presumptive diagnosis of pheochromocytoma in patients with nonepisodic hypertension Confirming positive plasma metanephrine results in patients with nonepisodic hypertension

Interpretation: Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Increased urine metanephrines can be detected in nonpheochromocytoma hypertensive patients; quantification may help distinguish these patients from those with tumor-induced symptoms.

Reference Values:

METANEPHRINE/CREATININE
Normotensives
0-2 years: 82-418 mcg/g creatinine
3-8 years: 65-332 mcg/g creatinine
9-12 years: 41-209 mcg/g creatinine
13-17 years: 30-154 mcg/g creatinine
> or =18 years: 29-158 mcg/g creatinine

NORMETANEPHRINE/CREATININE
Males
Normotensives
0-2 years: 121-946 mcg/g creatinine
3-8 years: 92-718 mcg/g creatinine
9-12 years: 53-413 mcg/g creatinine
13-17 years: 37-286 mcg/g creatinine
18-29 years: 53-190 mcg/g creatinine
30-39 years: 60-216 mcg/g creatinine
40-49 years: 69-247 mcg/g creatinine
50-59 years: 78-282 mcg/g creatinine
60-69 years: 89-322 mcg/g creatinine
> or =70 years: 102-367 mcg/g creatinine
Females
Normotensives
0-2 years: 121-946 mcg/g creatinine
3-8 years: 92-718 mcg/g creatinine
9-12 years: 53-413 mcg/g creatinine
13-17 years: 37-286 mcg/g creatinine
18-29 years: 81-330 mcg/g creatinine  
30-39 years: 93-379 mcg/g creatinine  
40-49 years: 107-436 mcg/g creatinine  
50-59 years: 122-500 mcg/g creatinine  
60-69 years: 141-574 mcg/g creatinine  
> or =70 years: 161-659 mcg/g creatinine

TOTAL METANEPHRINE/CREATININE

Males
Normotensives
0-2 years: 241-1,272 mcg/g creatinine
3-8 years: 186-980 mcg/g creatinine
9-12 years: 110-582 mcg/g creatinine
13-17 years: 78-412 mcg/g creatinine
18-29 years: 96-286 mcg/g creatinine
30-39 years: 106-316 mcg/g creatinine
40-49 years: 117-349 mcg/g creatinine
50-59 years: 130-386 mcg/g creatinine
60-69 years: 143-427 mcg/g creatinine
> or =70 years: 159-472 mcg/g creatinine

Females
Normotensives
0-2 years: 241-1,272 mcg/g creatinine
3-8 years: 186-980 mcg/g creatinine
9-12 years: 110-582 mcg/g creatinine
13-17 years: 78-412 mcg/g creatinine
18-29 years: 131-467 mcg/g creatinine
30-39 years: 147-523 mcg/g creatinine
40-49 years: 164-585 mcg/g creatinine
50-59 years: 184-655 mcg/g creatinine
60-69 years: 206-733 mcg/g creatinine
> or =70 years: 230-821 mcg/g creatinine

This test is for billing purposes only.
This is not an orderable test.

**M15**

**Metaphases, 15 (Bill Only)**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**M25**

**Metaphases, 20-25 (Bill Only)**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**ML15**

**Metaphases,**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**MG14**

**Metaphases, >15 (Bill Only)**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**MG19**

**Metaphases, >20 (Bill Only)**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**MG25**

**Metaphases, >25 (Bill Only)**

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**FMETN**

**Metformin, Plasma**

Reference Values:
Reporting limit determined each analysis.

Units: mcg/mL

Therapeutic range: Approximately 1-2 mcg/mL.
Metformin associated lactic acidosis generally has been associated with Metformin plasma concentrations exceeding 5 mcg/mL.
**Methadone and Metabolites, Serum**

**Clinical Information:** Methadone, a long-acting synthetic opioid analgesic, is an agonist at the mu receptor. It has several actions qualitatively similar to those of morphine, primarily involving the central nervous system and organs composed of smooth muscles. Analgesia, sedation, and detoxification or maintenance in opioid addiction can be achieved with therapeutic use of methadone hydrochloride.

Methadone acts by binding to the mu-opioid receptor but also has some affinity for the N-methyl-D-aspartate receptor (NMDA) ionotopic glutamate receptor. Methadone undergoes extensive biotransformation in the liver. Methadone is metabolized by cytochrome P450 (CYP) 3A4, CYP2B6, CYP2C19, and CYP2D6 enzymes. It is also a substrate for the P-glycoprotein efflux protein. The major inactive metabolite is a result of N-demethylation and cyclization, and forms 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Substantial interindividual and intraindividual variabilities in metabolism and elimination have been noted. The half-life of methadone is highly variable and typically ranges from 7 to 59 hours; however, longer half-lives have been reported.

**Useful For:** Compliance monitoring of methadone

**Interpretation:** There is a significant overlap between the reported therapeutic and toxic concentrations of methadone in blood specimens.

**Reference Values:**
Not established

**Clinical References:**

**Methadone Confirmation, Chain of Custody, Random, Urine**

**Clinical Information:** Methadone (dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin.(1) Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are cytochrome P450 (CYP) 3A4 and CYP2B6.(1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved.(1-5) Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl1-3,3-diphenylpyrrolidine (EDDP).(1-4) The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys.(1,4) Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH.(5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are therefore, preferable for assessing compliance with therapy.(5) Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine.(6) This is commonly referred to as “spiking.” In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP.(6) The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone.
to the specimen. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Monitoring for compliance of methadone treatment for analgesia or drug rehabilitation. Urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is particularly useful for assessing compliance with rehabilitation programs. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of >0.60. An EDDP: methadone ratio <0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cutoff Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMUNOASSAY SCREEN</td>
<td>&lt;300 ng/mL</td>
</tr>
<tr>
<td>METHADONE BY GC-MS</td>
<td>&lt;100 ng/mL</td>
</tr>
<tr>
<td>2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE BY GC-MS</td>
<td>&lt;100 ng/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**


**Methadone Confirmation, Random, Urine**

**Clinical Information:** Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin. Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are cytochrome P450 (CYP) 3A4 and CYP2B6. CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved. Methadone is metabolized to a variety of metabolites with the primary metabolite being...
2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys. Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH. EDDP levels, in contrast, are relatively unaffected by the influence of pH and are therefore preferable for assessing compliance with therapy. Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine. This is commonly referred to as "spiking." In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP. The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen.

**Useful For:** Monitoring for compliance of methadone treatment for analgesia or drug rehabilitation

**Assessing compliance with rehabilitation programs by urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine**

**Interpretation:** The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of greater than 0.60. An EDDP:methadone ratio less than 0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen.

**Reference Values:**

**Negative**

Cutoff concentrations:

- METHADONE BY GC-MS
  - <100 ng/mL
- 2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE GC-MS
  - <100 ng/mL

**Clinical References:**


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**Methaqualone Confirmation, urine**

**Interpretation:** Methaqualone, ng/mL. Report Limit 50 ng/mL. Reference Range 500-80000 ng/mL. Critical Value Acetaminophen High 160000 ng/mL.

**Reference Values:**

ng/mL

Results are reported to the limit of quantitation for the analysis.
**Methemoglobin and Sulfhemoglobin, Blood**

**Clinical Information:** Methemoglobin: When iron in hemoglobin is oxidized from the normal divalent state to a trivalent state, the resulting brownish pigment is methemoglobin. Methemoglobin cannot combine reversibly with oxygen and is associated with cyanosis. Methemoglobinemia, with or without sulfhemoglobinemia, is most commonly encountered as a result of administration of medications such as phenacetin, phenazopyridine, sulfonamides, local anesthetics, dapsone, or following ingestion of nitrites or nitrates. Congenital methemoglobinemias are rare. They are either due to: -Deficiency of methemoglobin reductase (also called cytochrome B5 reductase or diaphorase) in erythrocytes, an autosomal recessive disorder. -One of several intrinsic structural disorders of hemoglobin, called methemoglobin-M, all of which are inherited in the autosomal dominant mode. Methemoglobinemia responds to treatment with methylene blue or ascorbic acid. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. Sulfhemoglobinemia is associated with cyanosis and often accompanies drug-induced methemoglobinemia. Sulfhemoglobinemia can be due to exposure to trinitrotoluene or zinc ethylene bisdithiocarbamate (a fungicide), or by ingestion of therapeutic doses of flutamide. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, blood level of sulfhemoglobin declines gradually over a period of weeks. Patients with sulfhemoglobinemia often also have methemoglobinemia. There is no specific treatment for sulfhemoglobinemia. Therapy is directed at reversing the methemoglobinemia, if present.

**Useful For:** Diagnosing methemoglobinemia and sulfhemoglobinemia Identifying cyanosis due to other causes, such as congenital heart disease

**Interpretation:** In congenital methemoglobinemia, the methemoglobinemia concentration in blood is about 15% to 20% of total hemoglobin. Such patients are mildly cyanotic and asymptomatic. In acquired (toxic) methemoglobinemia, the concentration may be much higher. Symptoms may be severe when methemoglobin is >40% of hemoglobin. Very high concentrations (>70%) may be fatal.

**Reference Values:**

**METHEMOGLOBIN**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 months</td>
<td>not established</td>
</tr>
<tr>
<td>&gt; or =1 year</td>
<td>0.0-1.5% of total hemoglobin</td>
</tr>
</tbody>
</table>

**SULFHEMOGLOBIN**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 months</td>
<td>not established</td>
</tr>
<tr>
<td>&gt; or =1 year</td>
<td>0.0-0.4% of total hemoglobin</td>
</tr>
</tbody>
</table>


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**Methemoglobin Summary Interpretation**

**Clinical Information:** Hemoglobin variants can be associated with increased measured levels of methemoglobin and sulfhemoglobin. Some hemoglobin disorders can be very complex and involve abnormalities of the alpha, beta, delta, and gamma genes. These abnormalities can be due to, not only to point alterations, but also deletions within 1 or more globin genes. Multiple genetic variants can be seen in the same patient, and molecular testing is necessary to fully evaluate such cases. A summary interpretation that incorporates all of the testing performed is beneficial to the ordering physician.

**Useful For:** Incorporating and summarizing subsequent results into an overall evaluation if 1 or more molecular tests are reflexed on the MEV1 / Methemoglobinemia Evaluation

**Interpretation:** An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

**Reference Values:**
An interpretive report will be provided.


**Methemoglobinemia Evaluation, Blood**

**Clinical Information:** Methemoglobin: Methemoglobin forms when the hemoglobin (Hb) molecule iron is in the ferric (Fe3⁺) form instead of the functional ferrous (Fe2⁺) form. Methemoglobinemia can be hereditary or acquired and is present by definition when methemoglobin levels are greater than the normal range. Acquired methemoglobinemia results after toxic exposure to nitrates and nitrites/nitrates (fertilizer, nitric oxide), topical anesthetics (“caines”), dapsone, naphthalene (moth balls/toilet deodorant cakes), and industrial use of aromatic compounds (aniline dyes). Congenital methemoglobinemias are rare. They are due either to: - A deficiency of cytochrome b5 reductase (methemoglobin reductase) in erythrocytes, an autosomal recessive disorder resulting from genetic variants in either CYB5R3 or CYB5A.(1,2) Type IV is thought to be extraordinarily rare. Type III is no longer a category. - One of several intrinsic structural disorders of Hb, called M-Hbs; all of which are inherited in an autosomal dominant manner.(3,4) Classically, M-Hbs result from histidine-to tyrosine substitutions at the proximal or distal histidine important in coordinating the oxygen molecule. These include alpha-, beta- and gamma-chain variants. Rarely, other substitutions outside the proximal and distal histidine location can cause Hb variants that increase methemoglobin or sulfhemoglobin levels. Most M-Hb variants are readily identified by high performance liquid chromatography (HPLC) or mass spectrometry methods with characteristic electrophoresis patterns; however, some require more specialized techniques. Most are associated with increased methemoglobin with or without an increase in sulfhemoglobin. Alpha chain M-Hb variants can be associated with increased sulfhemoglobin without an increase in methemoglobin. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. When acquired, sulfhemoglobinemia can be associated with cyanosis and often accompanies methemoglobinemia. Sulfhemoglobinemia has been associated with exposure to sumatriptan, sulfonamides, metoclopramide, paint or varnish vapors, dimethyl sulfoxide (DMSO), acetanilide, phenacetin, trinitroluene, zinc ethylene bisdithiocarbamate (a fungicide), and flutamide. It is important to note that some Hb variants are known to interfere with this test (especially M-Hbs) and sulfhemoglobin absorbance can be increased due to the Hb variant. Hb evaluation that includes the HPLC method is recommended to exclude this possibility. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, blood level of sulfhemoglobin declines gradually over a period of weeks.

**Useful For:** Diagnosis of methemoglobinemia and sulfhemoglobinemia and possible hereditary (congenital) causes Differentiation of methemoglobinemia and sulfhemoglobinemia from other causes of cyanosis (eg, congenital heart disease)

**Interpretation:** This is a consultative evaluation in which the history and previous laboratory values are reviewed by a hematologist who is an expert on these disorders. Appropriate tests are performed and an interpretive report is issued.

**Reference Values:** Definitive results and an interpretive report will be provided.

**Clinical References:** 1. OMIM: 250800 Methemoglobinemia due to deficiency of methemoglobin
Methemoglobinemia Interpretation

Clinical Information: Methemoglobin: Methemoglobin forms when the hemoglobin molecule iron is in the ferric (Fe[3+]) form instead of the functional ferrous (Fe[2+]) form. Methemoglobinemia can be hereditary or acquired and is present by definition when methemoglobin levels are greater than the normal range. Acquired methemoglobinemia results after toxic exposure to nitrates and nitrites/nitrates (fertilizer, nitric oxide), topical anesthetics (“caines”), dapsone, naphthalene (moth balls/toilet deodorant cakes), and industrial use of aromatic compounds (aniline dyes). Congenital methemoglobinemas are rare. They are due either to: -A deficiency of cytochrome b5 reductase (methemoglobin reductase) in erythrocytes, an autosomal recessive disorder resulting from genetic variants in either CYB5R3 or CYB5A genes. (1,2) Type IV is thought to be extraordinarily rare. Type III is no longer a category. -One of several intrinsic structural disorders of hemoglobin, called M-hemoglobins (M-Hb), all of which are inherited in an autosomal dominant manner. (3,4) Classically, M-Hb result from histidine-to-tyrosine substitutions at the proximal or distal histidine important in coordinating the oxygen molecule. These include alpha-, beta- and gamma-chain variants. Rarely, other substitutions outside the proximal and distal histidine location can cause hemoglobin variants that increase methemoglobin or sulfhemoglobin levels. Most M-Hb variants are readily identified by high-performance liquid chromatography (HPLC) or mass spectrometry methods with characteristic electrophoresis patterns; however, some require more specialized techniques. Most are associated with increased methemoglobin, with or without an increase in sulfhemoglobin. Alpha chain M-Hb variants can be associated with increased sulfhemoglobin without an increase in methemoglobin. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. When acquired, sulfhemoglobinemia can be associated with cyanosis and often accompanies methemoglobinemia. Sulfhemoglobinemia has been associated with exposure to sumatriptan, sulfonamides, metoclopramide, paint or varnish vapors, dimethyl sulfoxide (DMSO), acetaldehyde, phentacain, trinitoluene, zinc ethylene bisdithiocarbamate (a fungicide), and flutamide. It is important to note that some hemoglobin variants are known to interfere with this test (especially M-Hb), and sulfhemoglobin absorbance can be increased due to the hemoglobin variant. Hemoglobin evaluation that includes the HPLC method is recommended to exclude this possibility. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, blood level of sulfhemoglobin declines gradually over a period of weeks.

Useful For: Interpretation of the methemoglobinemia evaluation results Diagnosis of methemoglobinemia and sulfhemoglobinemia and possible hereditary (congenital) causes Differentiation of methemoglobinemia and sulfhemoglobinemia from other causes of cyanosis (eg, congenital heart disease)

Interpretation: This is a consultative evaluation in which the history and previous laboratory values are reviewed by a hematologist who is an expert on these disorders. Appropriate tests are performed and an interpretive report is issued.
**MTXSG**

**Methotrexate Post Glucarpidase, Serum**

**Clinical Information:** Methotrexate, an antimetabolite (folate reductase inhibitor), is used at high dose (12 gm/m2) to treat neoplastic diseases, such as lymphocytic leukemia. Therapy is guided by measurement of serum concentration: 24 hours after dosage, the serum concentration should be less than 10 mcmol/L; 48 hours after dosage, concentration should be less than 1 mcmol/L; and 72 hours after dosage, the concentration should be less than 0.1 mcmol/L or less than 0.05 mcmol/L, depending on clinical protocol. It is also administered at low dose (a single dose of 5-15 mg per week) to treat severe psoriasis and rheumatoid arthritis. Methotrexate is 65% orally bioavailable. Peak serum concentrations are reached 2 to 3 hours after dosing. Protein binding is approximately 45%. Volume of distribution is 0.4 L/kg. Elimination is concentration dependent with an apparent elimination half-life of 1.8 hours when the serum concentration is above 1 mcmol/L, 8 hours when between 0.1 and 1 mcmol/L, and approximately 30 hours when below 0.1 mcmol/L. Voraxaze (glucarpidase) is a carboxypeptidase enzyme indicated for the treatment of toxic plasma methotrexate (MTX) concentrations (>1 mcmol/L) in patients with delayed methotrexate clearance due to impaired renal function. Measurement of methotrexate using immunoassays is unreliable for specimens collected within 48 hours following Voraxaze administration since it can result in falsely elevated results. As a result, this liquid chromatography-tandem mass spectrometry assay should be used to monitor MTX concentrations postglucarpidase therapy.

**Useful For:** Monitoring methotrexate concentrations postglucarpidase therapy

**Interpretation:** Following a 4 to 6 hour intravenous infusion of methotrexate, postinfusion concentrations greater than the following indicate an increased risk of toxicity if conventional low-dose leucovorin rescue is given: -24-hour postinfusion concentration: 5.0 to 10.0 mcmol/L -48-hour postinfusion concentration: 0.5 to 1.0 mcmol/L -72-hour postinfusion concentration: 0.1 mcmol/L

**Reference Values:**
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L

**Clinical References:**
Methotrexate, Serum

Clinical Information: Methotrexate is an antineoplastic agent that inhibits DNA synthesis. The medication exerts its effects through competitive inhibition of the enzyme dihydrofolate reductase thus decreasing the concentrations of tetrahydrofolate essential to the methylation of pyrimidine nucleotides and consequently the rate of pyrimidine nucleotide and ultimately DNA synthesis. Methotrexate is used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Methotrexate is effective against malignancies characterized by rapid cell proliferation. Intermediate to high doses of methotrexate with leucovorin (citrovorum-factor or folinic acid) rescue to salvage nontumor cells have been used with favorable results in the treatment of osteogenic sarcoma, leukemia, non-Hodgkin lymphoma, lung, and breast cancer. Methotrexate has the potential for serious toxicity. Patients undergoing methotrexate therapy are closely monitored so that toxic effects are detected promptly.

Useful For: Determining whether methotrexate is being cleared appropriately and verifying that a nontoxic concentration has been attained following therapy

Interpretation: Serum concentrations of methotrexate are commonly monitored during high-dose therapy (>50 mg/m[2]) to identify the time at which active intervention by leucovorin rescue should be initiated. Criteria for serum concentrations indicative of a potential for toxicity after single-bolus, high-dose therapy are as follows: -Methotrexate >10 mcmol/L 24 hours after dose -Methotrexate >1 mcmol/L 48 hours after dose -Methotrexate >0.1 mcmol/L 72 hours after dose

Reference Values:
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L

Clinical References:

Methsuximide (Celontin) as Desmethylmethsuximide

Reference Values:
10.0 - 40.0 ug/mL

Methsuximide measured as desmethylmethsuximide.

Methylmalonic Acid, Quantitative, Plasma

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births.
with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels. Several studies have suggested that the determination of plasma or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin deficiency.

**Reference Values:**
< or =0.40 nmol/mL

**Clinical References:**

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**Methylmalonic Acid, Quantitative, Serum**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired nutritional deficiencies are much more common than inherited defects and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In
adults, moderately elevated values indicate a likely cobalamin (vitamin B12) deficiency.

**Reference Values:**

< or =0.40 nmol/mL


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### MMAU 80290

**Methylmalonic Acid, Quantitative, Urine**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, which includes serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin deficiency

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin deficiency.

**Reference Values:**

<3.60 mmol/mol creatinine

Methylmalonic Aciduria and Homocystinuria, cblC Type, Full Gene Analysis, Varies

Clinical Information: Multiple causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 9 distinct complementation classes (cblA-cblH and mut, caused by variants in the gene encoding methylmalonyl coenzyme A mutase). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both. The most common disorder in this group is methylmalonic aciduria and homocystinuria, cblC (cobalamin C) type, which results in both methylmalonic aciduria and homocystinuria. cblC type is an autosomal recessive disorder with a variable age of onset. In the early onset form, symptoms appear in the first several years of life and include failure to thrive, developmental delay, seizures, metabolic crisis, and hydrocephalus. Patients may also have hemolytic uremic syndrome. Adults can present with confusion or other changes in mental status, cognitive decline, and megaloblastic anemia. Biochemical presentation includes methylmalonic aciduria and homocystinuria in urine organic acid or plasma amino acid analysis. Other complementation class disorders, such as cblD and cblF, can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types. Variants in the MMACHC gene are responsible for the cblC type disorder. The most common variant (identified in approximately 40% of variant alleles) is 271dupA. This multiethnic alteration is most frequently associated with early-onset disease, especially when present in the homozygous state. Another early-onset variant is R111X, which is common in the Cajun and French Canadian populations. R132X is a late-onset alteration that has been identified in individuals of Indian, Pakistani, and Middle Eastern ethnicity. Although these genotype-phenotype correlations are well-established, there is often considerable variability in age of onset and expression of symptoms, even within families.

Useful For: Confirmation of diagnosis of methylmalonic aciduria and homocystinuria, cblC type
Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified
Carrier screening in cases where there is a family history of methylmalonic aciduria and homocystinuria, but disease-causing variants have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Methylmalonic Aciduria and Homocystinuria, cblD Type, Full Gene Analysis, Varies

Clinical Information: Several causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 8 distinct
Complementation classes (cblA-cblH). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both. cblD type is a rare autosomal recessive disorder with variable clinical presentations. It can present as cblD variant 1, associated with isolated homocystinuria; cblD variant 2, associated with isolated methylmalonic aciduria; or as cblD combined, associated with both methylmalonic aciduria and homocystinuria. cblD variant 1 is associated with clinical features of isolated homocystinuria, including megaloblastic anemia and neurological abnormalities, as well as developmental delays. cblD variant 2 is associated with clinical features of isolated methylmalonic aciduria, including metabolic decomposition, which can result in lethargy, failure to thrive, feeding problems, and hypotonia. cblD combined is associated with clinical features of both methylmalonic aciduria and homocystinuria. Biochemical presentation includes methylmalonic aciduria and/or homocystinuria in urine organic acid or plasma amino acid analysis. (1) Other complementation class disorders can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types. Mutations in the MMADHC gene are responsible for the cblD type disorder. To date, 9 mutations in 7 individuals have been identified. (2) Three missense mutations identified in exons 6 and 8 have been associated with cblD variant 1. One nonsense mutation, 1 in-frame duplication, and 1 frame-shift deletion in exons 3 and 4 have been associated with cblD variant 2. One nonsense mutation, 1 frame-shift duplication, and 1 splice-site deletion in exons 5 and 8 and intron 7 have been associated with cblD combined.

**Useful For:** Confirmation of diagnosis of disorders belonging to the cblD complementation group Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified Distinguishing between cblA, cblB, and cblD variant 2 when methylmalonic aciduria is identified Distinguishing between cblD variant 1, cblE, and cblG when homocystinuria is identified Carrier screening in cases where there is a family history of methylmalonic aciduria or homocystinuria, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Methylmalonic Aciduria Gene Panel, Varies**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism. MMA is a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase caused by pathogenic variants in the mutase gene (MUT). Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin (Cbl) synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with methylmalonic

**MMAGP**

608021

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1692
acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels (MMAP / Methylmalonic Acid, Quantitative, Plasma and MMAU / Methylmalonic Acid, Quantitative, Urine). Plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Urine), and homocysteine (HCYSP / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum) are recommended first-tier biochemical tests to screen patients for methylmalonic acidemia. A comprehensive gene panel is a helpful tool to establish a targeted diagnosis for patients with suggestive clinical and biochemical features of methylmalonic acidemia. Treatment is most effective when tailored to the specific type of methylmalonic acidemia. For example, intramuscular injections of hydrocobalamin are critical in the treatment of Cbl C, whereas oral cyanocobalamin is effective for methylmalonic acidemia mutase subtypes as well as other cobalamin subtypes. Acute treatment for methylmalonic acidemia consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been successful in treating some patients.

Useful For: Follow up for abnormal biochemical results suggestive of a methylmalonic acidemia Establishing a molecular diagnosis for patients with methylmalonic acidemia Identifying variants within genes known to be associated with methylmalonic acidemia, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Urine), and homocysteine (HCYS / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum). Molecular genetic testing can be used to confirm a biochemical diagnosis for MMA or PA. Treatment is most effective when tailored to the specific type of MMA or PA. For example, intramuscular injections of hydrocobalamin are critical in the treatment of Cbl C, whereas oral cyanocobalamin is effective for MMA mutase subtypes as well as other cobalamin subtypes. Acute treatment for MMA and PA is similar, consisting of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been used with success in treating some patients with MMA or PA.

Useful For: Follow up for abnormal biochemical results suggestive of methylmalonic acidemia or propionic acidemia Establishing a molecular diagnosis for patients with methylmalonic acidemia or propionic acidemia Identifying variants within genes known to be associated with methylmalonic acidemia or propionic acidemia, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Methylphenidate and Metabolite, Random, Urine

Clinical Information: Methylphenidate (MPH) is utilized for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. MPH has two chiral centers and is marketed as a racemic mixture and as the active d-enantiomer of racemic methylphenidate. Although the exact mechanism of its action has not been fully defined, it blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron thus increasing the concentrations of these monoamines in the extraneural space. Methylphenidate is extensively metabolized to ritalinic acid, which is an inactive metabolite.

Useful For: Monitoring urine methylphenidate and ritalinic acid concentrations to assess compliance in patients

Interpretation: Methylphenidate has an oral bioavailability of 22% to 100% with peak concentrations occurring around 2 hours for instant release and approximately 5 to 6 hours for extended release formulations. The half-life of methylphenidate is 2 to 4 hours. Methylphenidate is extensively metabolized to ritalinic acid, which is an inactive metabolite. The half-life of ritalinic acid is about 3 to 4 hours. Only small quantities (<1%) of unchanged methylphenidate appear in the urine as most of the dose (60%-86%) is excreted in the urine as ritalinic acid. The presence of methylphenidate or ritalinic acid in the urine indicates the patient has taken methylphenidate in the past 1 to 2 days.

Reference Values: Negative

Cutoff concentrations:
Methylphenidate by LC-MS/MS: 10 ng/mL
Ritalinic Acid by LC-MS/MS: 50 ng/mL
**Clinical References:**


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**Methylphenidate, Serum**

**Reference Values:**

Reference Range: 5.0 - 20.0 ng/mL

**MTAP Immunostain, Tech Only**

**Clinical Information:** Methylthioadenosine phosphorylase (MTAP) is a 9p21.3 related protein involved in purine metabolism that plays a role in salvage of adenosine and methionine and is expressed in mesothelial cells. Deletion of the 9p21.3 chromosome region and loss of MTAP (or BCRA1 associated protein 1: BAP1) protein expression is a reliable marker for malignant mesothelioma diagnosis.

**Useful For:** Helpful in the diagnosis of malignant mesothelioma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


**Mexiletine, Serum**

**Reference Values:**

Reference Range: 50 - 150 ng/mL
Clinical Information: Mexiletine is a class I B antiarrhythmic with electrophysiologic properties similar to lidocaine and is useful in suppression of ventricular arrhythmias. The drug exhibits a high degree of oral bioavailability, is approximately 60% protein bound, and undergoes renal clearance at a rate of 10.3 mL/min/kg. Mexiletine has a volume of distribution of 9.5 L/kg at a half-life of 11 hours. Myocardial infarction and uremia reduce the rate of clearance and increase the half-life of mexiletine, requiring dosage adjustment guided by drug monitoring. Mexiletine toxicity occurs at concentrations above 2.0 mcg/mL (trough value) and is characterized by symptoms of nausea, hypotension, sinus bradycardia, paresthesia, seizures, intermittent left bundle branch block, and temporary asystole.

Useful For: Assessing achievement of optimal therapeutic concentrations Assessing potential toxicity

Interpretation: Optimal response to mexiletine occurs when the serum concentration is within the range of 0.8 to 2.0 mcg/mL (trough value).

Reference Values:
Trough Value
0.5-2.0 mcg/mL: Therapeutic concentration
>2.0 mcg/mL: Toxic concentration

Clinical References:

MGMT Promoter Methylation, Tumor

Clinical Information: Glioblastoma (WHO grade IV astrocytoma) is the most frequent malignant primary central nervous system tumor in adults. It has a very poor prognosis, with median survival of less than a year. Current standard of care consists of surgical resection followed by radiotherapy in addition to alkylating chemotherapy with temozolomide. MGMT (O6-methylguanine-DNA methyltransferase) is a DNA repair enzyme. This enzyme rescues tumor cells from alkylating agent-induced damage, and this leads to resistance to chemotherapy with alkylating agents. Epigenetic silencing of the MGMT gene by promoter methylation results in decreased MGMT protein expression, reduced DNA repair activity, and potential increased sensitivity to therapy. MGMT promoter methylation status has been most widely evaluated by methylation-specific PCR method, which is both sensitive and specific. In newly diagnosed glioblastomas, the presence of MGMT promoter methylation has been shown to be an independent favorable prognostic factor and a strong predictor of responsiveness to alkylating chemotherapy (ie, temozolomide). This is particularly relevant for elderly patients (>60 years), who usually have decreased tolerance for combined aggressive chemoradiation. For this group of patients, recent clinical trials have provided strong evidence supporting an alternative therapeutic strategy consisting of monotherapy with the alkylating agent temozolomide for patients whose tumors show MGMT promoter methylation and radiotherapy alone for patients whose tumors lack MGMT promoter methylation. Thus, in addition to the significant prognostic and predictive value, MGMT methylation status has emerged as a valuable biomarker to guide therapy decision making for newly diagnosed glioblastoma in elderly patients, preventing unnecessary treatment toxicities and costs. MGMT promoter methylation has been reported to high rates in oligodendrogliomas and astrocytomas of lower grade, in which they variably correlate with 1p19q codeletion and IDH mutations. Prognostic and predictive significance of MGMT promoter methylation status in these tumors has been shown in some studies, but not in others.

Useful For: Prognostication of newly diagnosed glioblastomas Identifying newly diagnosed glioblastomas that may respond to alkylating chemotherapy (ie, temozolomide) Guiding therapy decision making for newly diagnosed glioblastomas in elderly patients (>60 years)
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CERAM 606777**

**MI-Heart Ceramides, Plasma**

**Clinical Information:** MI-Heart Ceramides is a blood test that measures risk for adverse cardiovascular events and quantifies plasma ceramides. Plasma ceramides are predictors of adverse cardiovascular events resulting from unstable atherosclerotic plaque. Ceramides are complex lipids that play a central role in cell membrane integrity, cellular stress response, inflammatory signaling, and apoptosis. Synthesis of ceramides from saturated fats and sphingosine occurs in all tissues. Metabolic dysfunction and dyslipidemia results in accumulation of ceramides in tissues not suited for lipid storage. Elevated concentrations of circulating ceramides are associated with atherosclerotic plaque formation, ischemic heart disease, myocardial infarction, hypertension, stroke, type 2 diabetes mellitus, insulin resistance, and obesity. Three specific ceramides have been identified as highly linked to cardiovascular disease and insulin resistance: Cer16:0, Cer18:0, and Cer24:1. Individuals with elevated plasma ceramides are at higher risk of major adverse cardiovascular events even after adjusting for age, gender, smoking status, and serum biomarkers such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, C-reactive protein (CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2). Ceramide concentrations are reduced by current cardiovascular therapies including diet, exercise, statins, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

**Useful For:** Evaluating for the risk of major adverse cardiovascular events within the next 1 to 5 years

**Interpretation:** Elevated plasma ceramides are associated with increased risk of myocardial infarction, acute coronary syndromes, and mortality within 1 to 5 years. Ceramide Score Relative Risk
Risk Category 0-2 1.0 Lower 3-6 1.5 Moderate 7-9 2.2 Increased 10-12 3.5 Higher Score is based on trial data including >4000 subjects.

**Reference Values:**
MI-Heart Ceramide Risk Score:
0-2 Lower risk
3-6 Moderate risk
7-9 Increased risk
10-12 Higher risk

- Ceramide (16:0): 0.19-0.36 mcmol/L
- Ceramide (18:0): 0.05-0.14 mcmol/L
- Ceramide (24:1): 0.65-1.65 mcmol/L
- Ceramide (16:0)/(24:0): <0.11
- Ceramide (18:0)/(24:0): <0.05
- Ceramide (24:1)/(24:0): <0.45

Reference values have not been established for patients who are <18 years of age.

Note: Ceramide (24:0) alone has not been independently associated with disease and will not be

MLCPC
Microdissection, Laser Capture (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MPSF
Micropolyspora faeni, IgG Antibodies, Serum

Clinical Information: Micropolyspora faeni is one of the causative agents of hypersensitivity pneumonitis (HP). Other causative microorganisms include Thermoactinomyces vulgaris and Aspergillus fumigatus. The development of HP caused by Micropolyspora faeni is accompanied by an immune response to Micropolyspora faeni antigens with production of IgG antibodies. While the immunopathogenesis of HP is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.(1)

Useful For: Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Micropolyspora faeni

Interpretation: Elevated concentrations of IgG antibodies to Micropolyspora faeni, Thermoactinomyces vulgaris, or Aspergillus fumigatus in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

Reference Values:
0-12 years: < or =4.9 mg/L
13-18 years: < or =9.1 mg/L
>18 years: < or =13.2 mg/L

Microsatellite Instability, Tumor

Clinical Information: Somatic (tumor-specific) microsatellite instability (MSI) is assessed by this test. MSI is characterized by numerous alterations in a type of repetitive DNA called microsatellites and occurs as the result of an impaired DNA mismatch repair process. Impaired DNA mismatch repair is a key factor in tumorigenesis and can occur sporadically or as the result of a hereditary cancer predisposition called Lynch syndrome. Evaluation for MSI may be valuable for clinical decision making. Current data suggest that advanced stage solid tumors with defective DNA mismatch repair (MSI-H) are more likely to respond to treatment with immunotherapies such as anti-PD-1 therapies. Colon cancers that demonstrate defective DNA mismatch repair (MSI-H) have a significantly better prognosis compared to those with intact mismatch repair (MSS/MSI-L). Additionally, current data indicate that stage II and stage III patients with colon cancers characterized by the presence of defective mismatch repair (MSI-H) may not benefit from treatment with fluorouracil alone or in combination with leucovorin. These findings are most likely to impact the management of patients with stage II disease. MSI analysis, usually in combination with immunohistochemistry staining of the mismatch repair proteins, can also provide helpful diagnostic information in the context of evaluation for Lynch syndrome. See Lynch Syndrome Testing Algorithm in Special Instructions.

Useful For: Evaluation of tumor tissue to identify patients at high risk for having Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer Evaluation of tumor tissue for clinical decision-making purposes given the prognostic and therapeutic implications associated with microsatellite instability phenotypes

Interpretation: The report will include specimen information, assay information, and interpretation of test results. Microsatellite stable (MSS) is reported as MSS (0 or 1 of 7 markers demonstrating instability) or microsatellite instability-high (MSI-H) (2 or more of 7 markers demonstrating instability).

Reference Values: An interpretive report will be provided.


Microsporidia species, Molecular Detection, PCR, Varies

Clinical Information: Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and Encephalitozoon cuniculi and Encephalitozoon hellem that can infect the conjunctiva, respiratory tract,
and genitourinary system. Human infections have been reported most frequently in patients with AIDS, but also can occur in other immunocompromised patients, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae and Brachiola species can cause disseminated or organ-specific disease. This assay detects only the most common microsporidia, Enterocytozoon bieneusi and Encephalitozoon species, and not microsporidiosis due to other species. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Detection of Enterocytozoon bieneusi and Encephalitozoon species in fecal and urine specimens to support the clinical diagnosis of microsporidiosis

**Interpretation:** A positive result indicates the presence of Enterocytozoon bieneusi and Encephalitozoon species DNA and is consistent with an active or recent infection. Since microsporidia DNA may be present in feces or urine in the absence of clinical symptoms, results should be correlated with clinical presentation. A negative result indicates absence of detectable DNA from Enterocytozoon bieneusi and Encephalitozoon species in the specimen, but does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or may be sporadic. Other tests to consider in the evaluation of a patient presenting with acute or chronic watery diarrhea include cultures or specific assays for bacterial, viral, and parasitic pathogens.

**Reference Values:**

Negative

**Clinical References:**


**MTBS 81507**

**Microsporidia Stain, Varies**

**Clinical Information:** Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and Encephalitozoon cuniculi and Encephalitozoon hellem, which can infect the conjunctiva, respiratory tract, and genitourinary system. Human infections have been reported most frequently in patients with AIDS, but also can occur in other immunocompromised patients, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae and Brachiola species can cause disseminated or organ-specific disease. Diagnosis of microsporidiosis is traditionally performed by light microscopic examination of stool, urine, and other specimens using a strong trichrome (chromotrope 2R) stain for detection of the characteristic spores. Unfortunately, microscopic identification can be challenging due to the small size of the spores (1-4 micrometer) and their resemblance to yeast. Molecular detection using species-specific PCR offers improved sensitivity and specificity and is available for the microsporidia that cause the majority of intestinal and renal infections (ie, Encephalitozoon species and Enterocytozoon bieneusi). The microsporidia stain is reserved for use with other (nonstool and nonurine) specimen sources due to the variety of other species that may be detected outside of the intestinal tract and kidney. The antihelmintic drug, albendazole has been found effective in some infections due to Enterocytozoon bieneusi and Encephalitozoon (Septata) intestinalis.

**Useful For:** Diagnosis of extra-intestinal microsporidiosis involving the lung, skin, and other organs, particularly in immunocompromised hosts Diagnosis of ocular microsporidiosis

**Interpretation:** A positive result suggests an active or recent infection. Results should be correlated with the patient’s clinical presentation and immune status. A negative result indicates absence of detectable microsporidial spores in the specimen but does not always rule out ongoing microsporidiosis.
since the organism may be present at very low levels or shed sporadically.

**Reference Values:**
Negative
If positive, reported as Microsporidia detected

**Clinical References:**

**F MIDZ**

**Midazolam (Versed), serum**

**Reference Values:**
Reference Range: 50 - 600 ng/mL

**FM CG4**

**Milk Cow IgG4**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

**MILK**

**Milk, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to milk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**FMINT**

**Mint (Mentha Piperita) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

**FMIRT**

**Mirtazapine (Remeron)**

**Reference Values:**

Reference range: 4.0 – 40.0 ng/mL

Expected steady state trough mirtazapine concentrations in patients receiving recommended daily dosages: 4.0 – 40.0 ng/mL

Toxic range not established.

**ZW199**

**Misc Alfred I duPont Hospital for Children**

**Reference Values:**

Test Performed By: Alfred I. duPont Hospital for Children
Molecular Diagnostics Laboratory
1600 Rockland Road
Wilmington, DE 19803

**ZW152**

**Misc Baylor Cytogenetics Laboratory**

**Reference Values:**

Test performed by: Baylor Cytogenetics Laboratory
2450 Holcombe Blvd
Houston TX 770212024

**ZW201**

**Misc Baylor John Welsh Cardiovascular Diag Lab**

**Reference Values:**

Test Performed By: Baylor College of Medicine John Walsh
Cardiovascular Diagnostics Laboratory
Dept of Pediatric Cardiology
1102 Bates, FC.480.02
Houston, Texas 77030

**ZW204**

**Misc Cincinnati Childrens Hospital Medical Center**

**Reference Values:**

Test Performed By: Cincinnati Childrens Hospital Medical Ctr
Molecular Genetics Lab
Misc Medical Neurogenetics, LLC
Reference Values:
Test Performed By: Medical Neurogenetics Lab
5424 Glenridge Drive NE
Atlanta, GA  30342

Misc Monogram Biosciences, Inc.
Reference Values:
TEST PERFORMED BY: MONOGRAM BIOSCIENCES, INC.
345 OYSTER POINT BOULEVARD
SOUTH SAN FRANCISCO, CA  94080

Misc National Jewish Health Mycobacteriology Test
Reference Values:
Test Performed by: National Jewish Health Mycobacteriology Lab
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

Miscellaneous Alfred I duPont Gastroenterology
Reference Values:
Test Performed By:  Alfred I. duPont Hospital for Children
Nemours Children's Clinic
Division of Gastroenterology/Nutrition
Gastroenterology Laboratory
1600 Rockland Rd.-Research Bldg. Rm 250
Wilmington, DE  19803

Miscellaneous Ambry Genetics
Reference Values:
Test Performed by:  Ambry Genetics
100 Columbia No. 200
Aliso Viejo, CA 92656

Miscellaneous ARUP Testing
Reference Values:
Test Performed by: ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108
Miscellaneous Asuragen Clinical Services
Reference Values:
Test Performed by: Asuragen, Clinical Services
2150 Woodward St., Ste. 100
Austin, TX 78744-2026

Miscellaneous Athena Testing
Reference Values:
Test Performed by: Athena Diagnostics
200 Forest Street, 2nd floor
Marlborough, MA 01752

Miscellaneous Baylor Medical Genetics Laboratories
Reference Values:
Test Performed by: Baylor Medical Genetics Laboratories
2450 Holcombe Blvd.
Houston, TX 77021

Miscellaneous Biochemical Genetics Testing
Reference Values:
Per request this test was performed outside of our validated test conditions. These test results should not be used for treatment or clinical diagnostic purposes.

Miscellaneous Center for Genetic Testing at St. Francis
Reference Values:
Test Performed by: Center for Genetic Testing
St. Francis Hosp-Genetics Lab
6161 S. Yale Ave.
Tulsa, OK 74136

Miscellaneous Chemistry Testing, Varies
Reference Values:
Varies

Miscellaneous Child Hosp-Philadelphia
Reference Values:
Test Performed by: The Children's Hospital of Philadelphia
Main Bldg 5th Floor Rm 5NWS55
34th Street and Civic Center Blvd
Philadelphia, PA 19104

Miscellaneous Childrens Hospital of Colorado Testing
Reference Values:
Reference Values:
Test Performed by: Childrens Hospital of Colorado
13123 E 16th Ave
Aurora, CO 80045

ZW279 58083 Miscellaneous Cincinnati Children's Nephrology
Reference Values:
Test Performed by: Cincinnati Children's Nephrology
3333 Burnet Avenue
Cincinnati, OH 45229

ZW193 91601 Miscellaneous Connective Tissue Gene Tests Lab (CTGT)
Reference Values:
Test Performed By: Connective Tissue Gene Tests, LLC
6575 Snowdrift Road, Suite 106
Allentown, PA 18106

ZW212 91859 Miscellaneous Correlagen Diagnostics
Reference Values:
Test Performed By: Correlagen Diagnostics
3400 Computer Drive, Suite 100
Westborough, MA 01581

ZW130 90569 Miscellaneous DIANON Systems
Reference Values:
Varies
Test Performed by: DIANON Systems, Inc.
1 Forest Parkway
Shelton, CT 06484

ZW57 90496 Miscellaneous Esoterix Coagulation
Reference Values:
Varies
Test Performed by: Esoterix Coagulation
8490 Upland Dr
Suite 100
Englewood, CO 80112

ZW189 91561 Miscellaneous Esoterix Genetic Laboratories, LLC - NY Testing
Reference Values:
Test Performed by: Esoterix Genetic NY
521 West 57th Street
6th Floor
ZВ208  Miscellaneous Genetic Assays Inc.
Reference Values:
Test Performed By: Genetic Assays, Inc.
4711 Trousdale Drive
Suite 209
Nashville, TN 37220

ZВ182  Miscellaneous Genova Diagnostics
Reference Values:
Test Performed by: Genova Diagnostics
63 Zillico Street
Asheville, NC 28801-1074

ZВ218  Miscellaneous Harvard Medical School
Reference Values:
Test Performed by: Harvard Medical School and Partners Healthcare
Laboratory for Molecular Medicine,
Center for Genetics and Genomics
65 Landsdowne Street
Cambridge, MA 02139

ZВ173  Miscellaneous Joli Diagnostics, Inc.
Reference Values:
Test Performed by: Joli Diagnostic
2451 Wehrle Drive
Williamsville, NY 14221

ZВ241  Miscellaneous Knight Diagnostic Laboratories
Reference Values:
Test Performed by: Knight Diagnostic Laboratories
2525 S.W. 3rd Ave.
Portland, OR 97201-3098

ZВ266  Miscellaneous Machaon Diagnostics
Reference Values:
Test Performed by: Machaon Diagnostics, Inc.
3023 Summit St.
Oakland, CA 94609

ZВ207  Miscellaneous MD Anderson Cancer Center
Reference Values:
ZW79 90518

Miscellaneous Med Coll of WI

Reference Values:

Test Performed by: Medical College of WI
MACC Fund Research Center, Room 5035
Dr. Nita Salzman, M.D., Ph.D.
8701 Watertown Plank Road
Milwaukee, WI 53226

ZW2 99992

Miscellaneous MML Referral Test 2

Clinical Information: NA

Reference Values:
Varies with test

ZW3 99993

Miscellaneous MML Referral Test 3

Reference Values:
Vary with test requested.

ZW85 90524

Miscellaneous National Jewish Health

Reference Values:
Test Performed by: National Jewish Health
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

ZW129 75137

Miscellaneous Pacific Rim Pathology Medical Corp

Reference Values:
Test Performed by:  Pacific Rim Pathology Medical Corp.
5325 Metro St. STE A
San Diego, CA 92110-2608

ZW194 91602

Miscellaneous Prevention Genetics Lab

Reference Values:
Test Performed By: Prevention Genetics Lab
Diagnostics Lab
3700 Downwind Drive
Marshfield, WI 54449

ZW96 90535

Miscellaneous Quest Diagnostics Valencia
Clinical Information: Conventional cytogenetic studies can identify the presence of chromosome abnormalities and most mosaic conditions. In approximately 2% of these chromosomally abnormal cases, the genetic makeup of the chromosome abnormality can be identified, but not completely characterized, by conventional techniques alone. For malignant disorders, the proportion of specimens with unresolved chromosome abnormalities is much higher. Chromosomal microarray analysis (CMA) can detect copy number gain or loss of a chromosomal region but cannot identify the mechanism. FISH using gene-specific probes and various probe strategies can help characterize chromosome abnormalities. This includes abnormalities that cannot be accurately characterized by chromosome analysis or CMA such as unusual structural alterations, and unbalanced chromosome abnormalities such as deletions, duplications, and translocations. Scoring large numbers of interphase nuclei can more accurately establish the frequency of chromosome abnormalities and assess level of mosaicism.

Useful For: Resolution of unusual or complex structural alterations, questionable mosaicism, and unbalanced chromosome abnormalities that cannot be resolved by chromosome or chromosomal microarray analysis. Identifying gain, loss, or rearrangement of chromosome regions using gene or locus-specific probes.

Interpretation: An interpretive report will be provided.

New Haven, CT 06511

**ZW288**  75170  
**Miscellaneous UF Health Medical Lab-Shands Hospital**  
**Reference Values:**  
Test Performed by:  
UF Health Medical Lab-Shands Hospital  
Infectious Disease Pharmacokinetics Laboratory  
1600 SW Archer Rd., P4-30  
Gainesville, FL 32610

**ZW292**  75215  
**Miscellaneous UNC Center for AIDS Research Clinical Pharmacology & Analytical Chemistry Laboratory**  
**Reference Values:**  
Test Performed by:  
UNC CFAR Clinical Pharmacology and Analytical Chemistry Lab  
120 Mason Farm Road, CB# 7361  
1100 Genetic Medicine Building  
Chapel Hill, NC 27599

**ZW99**  90538  
**Miscellaneous Univ of AL Testing**  
**Reference Values:**  
Test Performed by:  
University of Alabama-Birmingham  
648 Kaul Building  
720 20th Street South  
Birmingham, AL 35233

**ZW210**  91857  
**Miscellaneous Univ of IA Molecular Otolaryngology**  
**Reference Values:**  
Test Performed By:  
Univ of IA Molecular Otolaryngology Research Laboratory  
5270 Carver Biomedical Research Building  
Iowa City, IA 52242

**ZW186**  91515  
**Miscellaneous University of Chicago Genetics Services**  
**Reference Values:**  
Test Performed by:  
University of Chicago Genetics Services  
5841 S. Maryland Ave.  
Room 035, M/C 0077  
Chicago, IL 60637

**ZW187**  91514  
**Miscellaneous University of Iowa Diagnostic Labs**  
**Reference Values:**  
Test Performed by:  
UI Diagnostic Laboratories  
Department of Pathology  
200 Hawkins Drive, Rm 5231 RCP  
Iowa City, IA 52242

Current as of June 14, 2021 12:13 pm CDT  
800-533-1710 or 507-266-5700 or mayocliniclabs.com  
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ZW61 Miscellaneous University of Minnesota Outreach Laboratory
Reference Values:
Test Performed by: Univ of MN Outreach Laboratories
420 Delaware St. S.E.
Minneapolis, MN 55455

ZW191 Miscellaneous University of Texas Health Center at Tyler
Microbiology
Reference Values:
Test Performed By: University of Texas Health Center
Department of Microbiology
11937 US Hwy 271
Tyler, TX 75708

ZW217 Miscellaneous University of Utah Genome Center
Reference Values:
Test Performed By: University of Utah Genome Center
20 South 2030 East
Biomedical Polymers Building 570
Room 308
Salt Lake City, UT 84112-9454

ZW282 Miscellaneous University of Washington Medical Center (UW
Virology Dept of Lab Medicine)
Reference Values:
Test Performed by: UW Virology Dept of Lab Medicine,
1616 Eastlake Ave E
Ste 320 BOX 358115
Seattle, WA 98102

ZW278 Miscellaneous University of Washington Medical
Center-Clinical Immunology Lab
Reference Values:
Test Performed by: University of Washington Medical Center-Clinical Immunology Lab
1959 NE Pacific St. Room NW220
Seattle, WA 98195-0001

ZW293 Miscellaneous UPMC Molecular and Genomic Pathology
Reference Values:
Test Performed by: UPMC Molecular and Genomic Pathology
3477 Euler Way
Pittsburgh, PA 15213
Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor

Clinical Information: Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant inherited cancer syndrome that predisposes individuals to the development of colorectal, endometrial, gastric, upper urinary tract, and other cancers. Individuals with HNPCC/Lynch syndrome have a germline mutation in 1 of several genes involved in DNA mismatch repair. The majority of mutations associated with HNPCC/Lynch syndrome occur in MSH2 and MLH1; however, mutations in MSH6 and PMS2 have also been identified. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC/Lynch syndrome. Typically, the first step is to evaluate tumors for the characteristics common to individuals with HNPCC/Lynch syndrome, which include microsatellite instability (presence of numerous alterations in a type of repetitive DNA called microsatellites) and loss of protein expression of 1 or more of the genes associated with HNPCC/Lynch syndrome. Microsatellite instability (MSI) and immunohistochemistry (IHC) are commonly interpreted together to evaluate risk for HNPCC/Lynch syndrome. High levels of MSI within a tumor are suggestive of defective DNA mismatch repair, however, this finding does not provide information about which gene is involved. IHC is a complementary testing strategy used to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in HNPCC/Lynch syndrome-related cancers. Loss of expression of 1 or more of these proteins within the tumor is helpful in identifying which corresponding genes to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (eg, financial concerns, specimen requirements). IHC alone can determine retention or loss of MLH1, MSH2, MSH6, and PMS2 protein expression. If all 4 proteins are present, the likelihood of HNPCC/Lynch syndrome is reduced, but not eliminated, because approximately 5% of tumors that display MSI also have normal protein expression for these 4 genes. Loss of 1 or more proteins by IHC is suggestive of defective DNA mismatch repair within the tumor and the likelihood of HNPCC/Lynch syndrome is increased. Germline testing (ie, mutation analysis) for the corresponding genes can then be performed to identify the causative germline mutation and allow for predictive testing of at risk individuals. Of note, loss of protein expression by IHC has also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1 and PMS2 are observed, the BRMLH / MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor test may also help to distinguish between a sporadic and germline etiology. It should be noted that this is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions for additional information.

Useful For: Evaluation of tumor tissue to identify patients at risk for having hereditary nonpolyposis colon cancer/Lynch syndrome

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

**MiTF Immunostain, Technical Component Only**

**Clinical Information:** Microphthalmia-associated transcription factor (MiTF) is produced by melanocytes and osteoclasts and can be useful in the classification of melanoma.

**Useful For:** Identification of melanomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**Mitochondrial Antibodies (M2), Serum**

**Clinical Information:** Antimitochondrial antibodies (AMA) are detectable by indirect immunofluorescence in more than 90% of patients with primary biliary cirrhosis (PBC), but this method also detects AMA of differing specificities in other diseases. The mitochondrial antigens recognized by AMA in patients' sera have been classified numerically as M1 through M9, with the M2 antigen complex recognized by AMA in sera from patients with PBC. M2 antigen is comprised of enzyme proteins of the 2-oxoacid dehydrogenase complex that are located on inner mitochondrial membranes. Included in this group of autoantigens are the pyruvate dehydrogenase complex, and 2-oxoglutarate dehydrogenase complex.

**Useful For:** Establishing the diagnosis of primary biliary cirrhosis

**Interpretation:** Positive results for antimitochondrial antibody (AMA) of M2 specificity are highly specific for primary biliary cirrhosis (PBC), and false-negative results are rare. A positive result for AMA of M2 specificity in a patient with clinical features of PBC is virtually diagnostic for this disease.

**Reference Values:**
- Negative: <0.1 Units
- Borderline: 0.1-0.3 Units
- Weakly positive: 0.4-0.9 Units
- Positive: > or =1.0 Units
  Reference values apply to all ages.

Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. First, it is the site of energy metabolism, without which aerobic metabolism and life as we know it would not be possible. Second, it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to variants in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involving virtually any organ system, and with widely varying severities. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to determine the exact sequence of the entire 16,569 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from variants in the mitochondrial genome (mtDNA). This includes certain types of myopathies and neuro-ophthalmologic diseases, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged fibers (MERRF), mitochondrial myopathy (MM), neurogenic muscle weakness, ataxia, retinitis pigmentosa (NARP), Leigh syndrome, Leber hereditary optic neuropathy (LHON), and chronic progressive external ophthalmoplegia (CPEO). In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayre or Pearson syndromes, are also detected. Variants in mitochondrial proteins that are encoded by genes in the nucleus, such as the enzymes of fatty acid oxidation, are not detected using this test. In contrast to variants in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial variants can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of altered mitochondria present with more severe disease than those with lower percentages of altered alleles. The sensitivity for the detection of altered alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%.

Useful For: Diagnosis of the subset of mitochondrial diseases that results from variants in the mitochondrial genome A second-tier test for patients in whom previous targeted gene variant analyses for specific mitochondrial disease-related genes were negative Identifying variants within genes of the mitochondrial genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. The degree of heteroplasmy of each single nucleotide or INDEL (insertion/deletion) variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Large deletions will be reported as either homoplasmic or heteroplasmic, but the degree of heteroplasmy will not be estimated, due to possible preferential amplification of the smaller deletion product by long-range PCR.

Reference Values: An interpretive report will be provided.

 Mitochondrial Nuclear Gene Panel by Next-Generation Sequencing (NGS), Varies

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to variants in either the mitochondrial genome or nuclear mitochondrial genes has been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to analyze 176 nuclear-encoded genes implicated in mitochondrial disease. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from variants in the nuclear encoded genes. This includes disorders of mitochondrial protein synthesis, disorders of coenzyme Q10 biosynthesis, disorders of the respiratory chain complexes and disorders of mtDNA maintenance (ie, mitochondrial DNA depletion disorders). See Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel in Special Instructions for details regarding the targeted genes identified by this test.

Useful For: Diagnosis of the subset of mitochondrial disease that results from variants in the nuclear-encoded genes. A second-tier test for patients in whom previous targeted gene variant analyses for specific mitochondrial disease-related genes were negative. Identifying variants within genes of the nuclear genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Mitochondrial Respiratory Chain Enzyme Analysis (ETC) - Skin Fibroblasts

Reference Values: A final report will be attached in Mayo Access.


**FMITO**

**Mitotane (Lysodren)**

**Reference Values:**

Units: ug/mL

Therapeutic and toxic ranges have not been established.

Usual therapeutic doses produce Mitotane serum concentrations of less than 100 ug/mL.

**MLH1I**

**MLH-1, Immunostain (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**MLH1Z**

**MLH1 Gene, Full Gene Analysis, Varies**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer: HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are below 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain/canonical nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious alterations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MLH1 and PMS2 are more likely to have a germline variant in the MLH1 gene.

**Useful For:** Determining whether absence of MLH1 protein, by immunohistochemistry in tumor tissue, is associated with a germline variant in the affected individual Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer Identification of familial MLH1 variant to allow for
predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BMLHH**
**MLH1 Hypermethylation Analysis (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MLHPB**
**MLH1 Hypermethylation Analysis, Blood**

**Clinical Information:** Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome/HNPCC, as this leads to inactivation of the MSH2 promoter. Lynch syndrome/HNPCC is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome/HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome/HNPCC spectrum. Several clinical variants of Lynch syndrome/HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome/HNPCC. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and/or immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is
involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective mismatch repair in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. However, individuals with tumor hypermethylation may additionally have MLH1 promoter hypermethylation consistent with germline inactivation. Individuals with germline inactivation of MLH1 by promoter hypermethylation are at an increased risk for Lynch syndrome/HNPCC-related tumors. In contrast to sequence mutations in MLH1, current evidence suggests that the risk of transmitting germline MLH1 promoter hypermethylation is <50%.

**Useful For:** As an adjunct to positive hypermethylation in tumor to distinguish between somatic and germline hypermethylation As an adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates microsatellite instability-H (MSI-H) and loss of MLH1 protein expression

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Interpretive report will be provided.

**Clinical References:**

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**ML1HM**

**MLH1 Hypermethylation Analysis, Tumor**

**Clinical Information:** Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in one of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6, and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPCC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any one of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic
information when evaluating an individual suspected of having HNPCC/Lynch syndrome, especially when testing is performed in conjunction with MSI / Microsatellite Instability (MSI), Tumor and Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor studies. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions.

**Useful For:** An adjunct to MSI / Microsatellite Instability (MSI), Tumor and Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor when colon or endometrial tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing An adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates MSI-H and loss of MLH1 protein expression

**Interpretation:** An interpretive report will be provided. The likelihood of a germline (inherited) mutation is very low in those cases where the tumor demonstrates MLH1 promoter hypermethylation and the normal tissue is unmethylated. The likelihood of a germline mutation is high in those cases where the tumor and normal tissue lack MLH1 promoter hypermethylation. In cases where the tumor and normal tissue demonstrate MLH1 promoter hypermethylation, this result will be interpreted as equivocal and a blood sample will be requested to confirm potential germline hypermethylation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**BRMLH**

**MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor**

**Clinical Information:** Lynch syndrome is an inherited cancer syndrome caused by a germline pathogenic variant in one of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6, and PMS2. There are several laboratory-based strategies that help establish the diagnosis of Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any one of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) etiology, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific alteration in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E alteration is rarely identified in cases with germline MLH1 pathogenic variants. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E alteration can be used to help distinguish between germline etiology and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E alteration and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited (germline) pathogenic variant. Although testing for the BRAF V600E alteration and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having Lynch...
syndrome, especially when testing is performed in conjunction with MSI / Microsatellite Instability (MSI), Tumor and IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions.

**Useful For:** An adjunct to MSI / Microsatellite Instability (MSI), Tumor and IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor testing, when colon tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing in cases where colon tumor from the same patient demonstrates MSI-H and loss of MLH1 protein expression.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MLH1 Immunostain, Technical Component Only**

**Clinical Information:** Hereditary nonpolyposis colorectal cancer (HNPPC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. Testing tumors from individuals at risk for Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by Lynch syndrome usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have Lynch syndrome or somatic hypermethylation of MLH1.
Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this Lynch syndrome screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPPC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. Ä The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Ä Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**MLYCZ**

**MLYCD Gene, Full Gene Analysis, Varies**

**Clinical Information:** Malonyl-coenzyme A decarboxylase (MCD) deficiency is a rare autosomal...
recessive inborn error of fatty acid metabolism characterized by reduced activity of mitochondrial malonyl-CoA decarboxylase. This enzyme is responsible for conversion of intramitochondrial malonyl-CoA to acetyl-CoA and carbon dioxide. This leads to an accumulation of malonyl-CoA, which is a strong inhibitor of carnitine palmitoyltransferase-I (CPT-I), an enzyme active in beta-oxidation of fatty acids. The resulting effect is impairment of the breakdown of fatty acids. Isoforms of CPT-I have been found in skeletal and heart muscle, liver, and brain, and symptoms seem to correlate with the localization of these isoforms. The phenotype associated with MCD deficiency is variable, but may include developmental delay, seizures, hypotonia, metabolic acidosis, hypoglycemia, ketosis, and cardiomyopathy. The diagnosis of MCD deficiency is based on the findings of high urinary excretion of malonic acid and a mild increase in dicarboxylic acid. Acylcarnitine analysis by tandem mass spectrometry shows high blood levels of malonylcarnitine (C3DC), which can be detected by neonatal screening before the appearance of symptoms. Determination of MCD activity in cultured fibroblasts can confirm the diagnosis, although this testing is not currently clinically available in the United States. Mutations in the MLYCD gene are responsible for MCD deficiency. The MLYCD gene is located on chromosome 16 and has 5 coding exons. Several different mutations have been described including missense, nonsense, small insertions and deletions, as well as large genomic deletions.

**Useful For:** Confirmation of diagnosis of malonyl-CoA decarboxylase deficiency Carrier screening in cases where there is a family history of malonyl-CoA decarboxylase deficiency, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MOC31 Immunostain, Technical Component Only**

**Clinical Information:** antigen stains tumors of epithelial origin, adenocarcinomas, papillary serous carcinoma, breast, lung, prostate, and cholangiocarcinoma, among others. MOC31 may be used as part of a panel of stains to rule-out mesothelioma and support the diagnosis of carcinoma.

**Useful For:** Marker of epithelial cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Pai RK, West RB: MOC31 Exhibits Superior Reactivity Compared with Ber-EP4 in
MOLD Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mold Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-0.34</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Molecular Interpretation**

**Clinical Information:** Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal level Normal BPOM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels and normal p50 values (see Table).

**Useful For:** Interpretation of the hereditary erythrocytosis profile

**Interpretation:** An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variations in the gene. If positive, the variant will be correlated with clinical significance, if known.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

**Clinical References:**
Molybdenum, Blood

Clinical Information: Molybdenum is an essential trace element and a component of metalloflavoproteins. High concentrations are found in leafy vegetables and legumes. The recommended daily dietary allowance for molybdenum is 45 mcg for adults. As an industrial metal, molybdenum is used in the manufacturing of steel alloys, lubricants, or pigments. Occupational exposure is generally from inhalation of dusts or fumes. The current threshold limit is 0.5 mg/m³ for soluble compounds and 3 mg/m³ (respirable fraction) for the metal and its insoluble compounds. Oral absorption varies from 28% to 77%. Whole blood concentrations averaged 0.43 mcg/L (range 0.6-4.0 mcg/L) in unexposed individuals. However, exposed adults averaged 2.7 mcg/L (range 1.2-4.8 mcg/L). Once absorbed, molybdenum is primarily eliminated in the urine over 5 or more days. Molybdenum deficiency can cause irritability, altered levels of consciousness, and a variety of biochemical abnormalities. Toxicity can range from auditory and visual hallucinations, diarrhea, insomnia, painful extremities, and seizures.

Useful For: Determining molybdenum toxicity

Interpretation: Normal blood concentrations are 0.6-4.0 ng/mL in unexposed individuals and 1.2-4.8 ng/mL in exposed individuals.

Reference Values:

- <4 ng/mL (unexposed)
- <5 ng/mL (exposed)

MOLPS
Molybdenum, Serum

Clinical Information: Molybdenum is an essential trace element found in the daily diet. It is a cofactor for some enzymes important in nitrogen metabolism (aldehyde dehydrogenase, xanthine oxidase, NADH dehydrogenase). Due to the wide distribution of molybdenum in the environment and particularly in plant materials, molybdenum deficiency is rare in adults with normal, diverse diets. Typical molybdenum intake in most geographic locations is between 45 and 90 mcg/day. Urine is the primary source of excretion, though excesses are sometimes excreted by the biliary route. Molybdenum deficiency associated with parenteral nutrition is indicated by symptoms such as stunted growth, reduced appetite, tachycardia, tachypnea, blindness and coma. These symptoms can be corrected by introducing molybdenum supplementation. Molybdenum cofactor disease is a severe genetic disorder that is due to defective mutations in the MOCS1, MOCS2, and GEPH genes. Molybdenum toxicity is rare and usually related to molybdenum mining exposure; however, it has been observed in cases of intake above 400 mcg/day. Molybdenum interferes with copper uptake; molybdenum toxicity is predominantly due to copper deficiency (hypochromic anemia and neutropenia) and inhibition of xanthine oxidase (uric acid accumulation). Serum molybdenum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring of parenteral nutrition Monitoring metallic prosthetic implant wear As an indicator of molybdenum cofactor disease

Interpretation: Prosthesis wear is known to result in increased circulating concentrations of metal ions.(1 Serum concentrations above 10 ng/mL in a patient with molybdenum-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. Serum molybdenum levels below 0.3 ng/mL indicate potential deficiency. Increased serum molybdenum may be seen in acute viral hepatitis, chronic active hepatitis, alcoholic liver disease, and other forms of liver inflammation.

Reference Values:
0.3-2.0 ng/mL

Clinical References:
5. Reiss J, Johnson J: Mutations in the molybdenum cofactor biosynthetic genes MOCS1, MOCS2, and GEPH. Hum Mutat 2003;21(6):569-576

DMOGA
Monoclonal Gammopathy, Diagnostic, Serum

Clinical Information: Monoclonal proteins are markers of plasma cell proliferative disorders. The International Myeloma Working Group guidelines state that to adequately screen for a monoclonal protein, serum protein electrophoresis (SPE), immunofixation electrophoresis, and a serum free light chain (FLC) analysis should all be used. If amyloidosis is suspected, a 24-hour urine monoclonal protein study should be performed. The detection of M-proteins by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) has shown to be more analytically and clinically sensitive than immunofixation. In addition, the MALDI-TOF method can detect glycosylated light chains that have been demonstrated to be a risk factor for amyloidosis. This expanded monoclonal protein testing panel provides the highest diagnostic sensitivity for the monoclonal light chain diseases such as primary amyloidosis and light chain deposition disease; disorders that often do not have...
serum monoclonal proteins in high enough concentration to be detected and quantitated by SPE. The FLC assay is specific for free kappa and lambda light chains and does not recognize light chains bound to intact immunoglobulin. Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or B lymphocytes (multiple myeloma: MM, macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance: MGUS, smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other laboratory and clinical assessments. If a monoclonal protein pattern is detected by MALDI-TOF MS, immunofixation electrophoresis (IFE), or FLC, a diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been diagnosed, the size of the clonal abnormality can be monitored by SPE or FLC and, in some instances, by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of MGUS, the monoclonal gammopathy screen provides the information (size of M-spike, monoclonal protein isotype, FLC kappa/lambda ratio) needed for a MGUS progression risk assessment (see Interpretation).

Useful For: Screening and diagnosis of monoclonal gammopathies including analysis of free light chains Assessing the risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma

Interpretation: Monoclonal Gammopathies: - A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present. - A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). - A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. - A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. - An abnormal serum free light chain (FLC) kappa/lambda (K/L) ratio in the presence of a normal MALDI-TOF MS suggests a monoclonal light chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, a VISCS / Viscosity, Serum should be tested to rule out hyperviscosity syndrome. After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be a more useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS or FLC. Accordingly, a normal serum SPE does not rule out the disease and SPE alone should not be used to screen for the disorder if the clinical suspicion is high. MGUS Prognosis: - Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%. - High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal SPE Findings: - A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. - A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. - A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - In the hereditary deficiency of a protein (eg,
agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

**Reference Values:**

**TOTAL PROTEIN:**
- > or =1 year: 6.3-7.9 g/dL
- Reference values have not been established for patients that are <12 months of age.

**PROTEIN ELECTROPHORESIS**
- Albumin: 3.4-4.7 g/dL
- Alpha-1-globulin: 0.1-0.3 g/dL
- Alpha-2-globulin: 0.6-1.0 g/dL
- Beta-globulin: 0.7-1.2 g/dL
- Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report. Reference values have not been established for patients that are <16 years of age.

**M-PROTEIN ISOTYPE MALDI-TOF MS**
- No monoclonal protein detected
- M-protein Isotype MALDI-TOF MS Flag Negative

**KAPPA-FREE LIGHT CHAIN**
- 0.33-1.94 mg/dL

**LAMBDA-FREE LIGHT CHAIN**
- 0.57-2.63 mg/dL

**KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO**
- 0.26-1.65

**Clinical References:**
found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Immunoaffinity purification followed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPEP should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL respectively, should be followed by VISC / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal SPE patterns. Approximately 11% of patients with MM have a completely normal SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE, but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and should not be used to screen for the disorder. DMOGA / Monoclonal Gammopathy, Diagnostic, Serum, which includes MALDI-TOF MS and serum free light chains, conforms to the International Myeloma Working Group (IMWG) guidelines for screening and should be performed if there is clinical suspicion. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:
TOTAL PROTEIN:
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS:
Albumin: 3.4-4.7 g/dL
Alpha 1-Globulin: 0.1-0.3 g/dL
Alpha 2-Globulin: 0.6-1.0 g/dL
Beta-Globulin: 0.7-1.2 g/dL
Gamma-Globulin: 0.6-1.6 g/dL
An interpretive comment is provided.
Reference values have not been established for patients that are <16 years of age.


MPSU
Monoclonal Protein Study, 24 Hour, Urine
Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis:
Albumin - Alpha-1 - Alpha-2 - Beta-globulin - Gamma-globulin

The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available in Special Instructions:

Laboratory Approach to the Diagnosis of Amyloidosis - Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Monitoring patients with monoclonal gammopathies using 24-hour urine specimens

**Interpretation:** A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration is followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin free light chains as well as heavy chain fragments may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) or light chain deposition disease (LCDD).

Because patients with AL or LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

**Reference Values:**

**PROTEIN, TOTAL**

<229 mg/24 hours

Reference values have not been established for patients <18 years of age. Reference value applies to 24-hour collection.

**ELECTROPHORESIS, PROTEIN**

The following fractions, if present, will be reported as mg/24 hours:

- Albumin
- Alpha-1 globulin
- Alpha-2 globulin
- Betaglobulin
- Gamma globulin


**Monoclonal Protein Study, Expanded Panel, Serum**

**Clinical Information:** Monoclonal proteins are markers of plasma cell proliferative disorders. It has been recommended that serum and urine protein electrophoresis (PEL) and immunofixation electrophoresis (IFE) be performed as the diagnostic algorithm. A monoclonal band (M-spike) on serum or urine PEL identifies a monoclonal process and quantitates the abnormality. IFE characterizes the type of monoclonal protein (gamma, alpha, mu, delta, or epsilon heavy chain; kappa [K] or lambda [L] light chain). IFE is also more sensitive than PEL for detecting small abnormalities that may be present in diseases such as light chain multiple myeloma, oligosecretory myeloma, and plasmacytomas. With the addition of the serum free light chain (FLC) assay, the expanded monoclonal protein study provides even more diagnostic sensitivity for the monoclonal light chain diseases such as primary amyloid and light chain deposition disease; disorders that often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by PEL. The FLC assay is specific for free kappa and lambda light chains and does not recognize light chains bound to intact immunoglobulin. Importantly, the addition of the serum FLC assay to serum PEL and IFE makes the serum diagnostic studies sufficiently sensitive so that urine specimens are no longer required as part of initial diagnostic studies. Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or...
B lymphocytes (multiple myeloma: MM, macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance: MGUS, smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other laboratory and clinical assessments. If a monoclonal protein pattern is detected by IFE or FLC, a diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been diagnosed, the size of the clonal abnormality can be monitored by PEL and/or FLC and in some instances by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of MGUS, the expanded monoclonal protein study panel provides the information (size of M-spike, monoclonal protein isotype, FLC K/L ratio) needed for a MGUS progression risk assessment (see Interpretation).

**Useful For:** Diagnosis of monoclonal gammopathies Eliminating the need for urine monoclonal studies as a part of initial diagnostic studies (ie, rule-out monoclonal gammopathy) Assessing risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma

**Interpretation:** Monoclonal Gammopathies: - A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein. Immunofixation electrophoresis (IFE) is performed to identify the immunoglobulin heavy chain and/or light chain. - A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). - A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. - A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. - An abnormal serum free light chain (FLC) kappa/lambda (K/L) ratio in the presence of a normal IFE suggests a monoclonal light chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCs / Viscosity, Serum. - After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. - Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value. - Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IFE. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IFE and/or FLC. Accordingly, a normal serum PEL does not rule out the disease and PEL alone should not be used to screen for the disorder if the clinical suspicion is high. MGUS Prognosis: - Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%. - High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal PEL Findings: - A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. - A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. - A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypalbuminemia), the affected fraction is faint or absent. - An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

**Reference Values:**
PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
M-Spike: 0.0 g/dL
An interpretive comment is provided with the report.

IMMUNOFIXATION
No monoclonal protein detected

IMMUNOFIXATION FLAG
Negative

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO
0.26-1.65

Clinical References:

RMPSU
60069
Monoclonal Protein Study, Random, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis:
-Albumin  -Alpha-1  -Alpha-2  -Beta-globulin  -Gamma globulin The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammapathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The following algorithms are available in Special Instructions:
-Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

Useful For: Diagnosing monoclonal gammapathies

Interpretation: A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammapathies. The initial identification of an M-spike or an area of restricted migration is followed by immunofixation to identify the immunoglobulin heavy chains and light chains. Immunoglobulin free light chains as well as heavy chain fragments may be seen in the urine of patients.
with monoclonal gammopathies. The presence of a monoclonal light-chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) or light-chain deposition disease (LCDD). Because patients with AL or LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

Reference Values:
PROTEIN, TOTAL:
No reference values apply to random urine.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as mg/dL:
- Albumin
- Alpha-1 globulin
- Alpha-2 globulin
- Beta globulin
- Gamma globulin

Clinical References:
greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. -After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. -Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and PEL should not be used to screen for the disorder. Other Abnormal PEL Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent.

**Reference Values:**

**PROTEIN, TOTAL**

> or =1 year: 6.3-7.9 g/dL

Reference values have not been established for patients that are <12 months of age.

**PROTEIN ELECTROPHORESIS**

- Albumin: 3.4-4.7 g/dL
- Alpha-1-globulin: 0.1-0.3 g/dL
- Alpha-2-globulin: 0.6-1.0 g/dL
- Beta-globulin: 0.7-1.2 g/dL
- Gamma-globulin: 0.6-1.6 g/dL
- M-Spike: 0.0 g/dL

An interpretive comment is provided with the report.

**IMMUNOFIXATION**

No monoclonal protein detected

**IMMUNOFIXATION FLAG**

Negative

**Clinical References:**


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**MONOF 610018**

**Monocyte Repartition by CD14/CD16, Blood**

**Clinical Information:** Chronic myelomonocytic leukemia (CMML) is a myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap syndrome characterized by peripheral blood
monocytosis (absolute monocyte count \( \geq 1.0 \times 10^9/L \)), or \( \geq 10\% \) of the total white blood cell count) persisting for 3 months or greater. It could be very challenging to distinguish CMML from a reactive monocytosis or from a MPN (such as primary myelofibrosis or polycythemia vera) with monocytosis. Monocytes can be classified into 3 subsets: classical MO1 (CD14+/CD16-), intermediate MO2 (CD14+/CD16+), and non-classical MO3 (CD14-/CD16+) monocytes, with MO1 constituting the major monocyte population (85\%) in healthy individuals. Recent reports using multiparametric flow cytometry have demonstrated a characteristic increase in classical monocytes (>94\%) in CMML patients, thus distinguishing them from other causes of reactive and clonal monocytosis with greater than 90\% sensitivity and specificity. (1) This panel is designed to analyze the repartition of monocytes in these patients and to give a semi-quantitative value for the MO1 compartment. This value will aid in the differential diagnosis and monitoring of CMML.

**Useful For:** Aiding in the diagnosis and monitoring of chronic myelomonocytic leukemia (CMML)

**Interpretation:** An interpretive report describing the classical monocytes (MO1) fraction as either increased or normal will be provided. See Cautions.

**Reference Values:**
- % Monocytes of WBC: 1.0-6.6\%
- MO1 (classical monocytes): <94.0\%

**Clinical References:**

**MAAPC**
**Morph Analysis, Automated (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MAMPC**
**Morph Analysis, Manual (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MAIPC**
**Morph Analysis, Manual, IS (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MANPC**
**Morph Analysis, Nerve (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
Morphine Confirmation, Serum

Reference Values:
- Report Limit: 1 ng/mL
- Reference Range: 21-65 ng/mL

Morphology Evaluation (Special Smear), Blood

Clinical Information: Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count and special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.

Useful For: Detecting disease states or syndromes of the white blood cells, red blood cells, or platelet cell lines of a patient's peripheral blood

Interpretation: The laboratory will provide an interpretive report of percentage of white cells and, if appropriate, evaluation of white cells, red cells, and platelets.

Reference Values:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Neutrophils/bands</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Metamyelocytes</th>
<th>Myelocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>22-51%</td>
<td>37-73%</td>
<td>2-11%</td>
<td>1-4%</td>
<td>0-2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4-7 years</td>
<td>30-65%</td>
<td>29-65%</td>
<td>2-11%</td>
<td>1-4%</td>
<td>0-2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>8-13 years</td>
<td>35-70%</td>
<td>23-53%</td>
<td>2-11%</td>
<td>1-4%</td>
<td>0-2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Adults</td>
<td>50-75%</td>
<td>18-42%</td>
<td>2-11%</td>
<td>1-3%</td>
<td>0-2%</td>
<td>&lt;1%</td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>

An interpretive report will be provided.
Mosquito Species, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mosquito species Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to moth Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
</table>

Reference values apply to all ages.


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**FMONP 75067 Motor Neuropathy Panel**

**Reference Values:**

- **Asialo-GM1 Antibodies, IgG/IgM**
  - 29 IV or less: Negative
  - 30-50 IV: Equivocal
  - 51-100 IV: Positive
  - 101 IV or greater: Strong Positive

- **GM1 Antibodies, IgG/IgM**
  - 29 IV or less: Negative
  - 30-50 IV: Equivocal
  - 51-100 IV: Positive
  - 101 IV or greater: Strong Positive

- **GD1a Antibodies, IgG/IgM**
  - 29 IV or less: Negative
  - 30-50 IV: Equivocal
  - 51-100 IV: Positive
  - 101 IV or greater: Strong Positive
GD1b Antibodies, IgG/IgM
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

GQ1b Antibodies, IgG/IgM
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

Ganglioside (Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b) Antibodies, IgG/IgM:

Ganglioside antibodies are associated with diverse peripheral neuropathies. Elevated antibody levels to ganglioside-monosialic acid (GM1), and the neutral glycolipid, asialo GM1 are associated with motor or sensorimotor neuropathies, particularly multifocal motor neuropathy. Anti-GM1 may occur as IgM (polyclonal or monoclonal) or IgG antibodies. These antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals. GD1a antibodies are associated with different variants of Guillain-Barre syndrome (GBS) particularly acute motor axonal neuropathy while GD1b antibodies are predominantly found in sensory ataxic neuropathy syndrome. Anti-GQ1b antibodies are seen in more than 80 percent of patients with Miller-Fisher syndrome and may be elevated in GBS patients with ophthalmoplegia. The role of isolated anti-GM2 antibodies is unknown. These tests by themselves are not diagnostic and should be used in conjunction with other clinical parameters to confirm disease.

Total Protein, Serum
6.00-8.30 g/dL

Albumin
3.75-5.01 g/dL

Alpha-1 Globulins
0.19-0.46 g/dL

Alpha-2 Globulins
0.48-1.05 g/dL

Beta Globulins
0.48-1.10 g/dL

Gamma
0.62-1.51 g/dL

Immunoglobulin A
0 - 2 years: 2 - 126 mg/dL
3 - 4 years: 14 - 212 mg/dL
5 - 9 years: 52 - 226 mg/dL
10 - 14 years: 42 - 345 mg/dL
15 - 18 years: 60 - 349 mg/dL
19 years and older: 68 - 408 mg/dL

Immunoglobulin G
0 - 2 years: 242 - 1108 mg/dL
3 - 4 years: 485 - 1160 mg/dL
5 - 9 years: 514 - 1672 mg/dL
10 - 14 years: 581 - 1652 mg/dL
15 - 18 years: 479 - 1433 mg/dL
19 years and older: 768 - 1632 mg/dL
Immunoglobulin M
0 - 2 years: 21 - 215 mg/dL
3 - 4 years: 26 - 155 mg/dL
5 - 9 years: 26 - 188 mg/dL
10 - 14 years: 47 - 252 mg/dL
15 - 18 years: 26 - 232 mg/dL
19 years and older: 35-263 mg/dL

Myelin Associated Glycoprotein (MAG) Antibody, IgM
Less than 1000 TU

An elevated IgM antibody concentration greater than 999 TU against myelin-associated glycoprotein (MAG) suggests active demyelination in peripheral neuropathy. A normal concentration (less than 999 TU) generally rules out an anti-MAG antibody-associated peripheral neuropathy.

TU= Titer Units

CED
82668

Mountain Cedar, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mountain cedar Defining the allergen responsible for eliciting signs and symptoms Identifying allergens - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>

**MOUS 82707**

**Mouse Epithelium, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to mouse epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**MOSP 82792**

**Mouse Serum Protein, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages.

clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to mouse serum protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
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Reference values apply to all ages.


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**Movement Disorder, Autoimmune Evaluation, Serum**

**Clinical Information:** Autoimmune movement disorders encapsulate a large and diverse group of neurologic disorders occurring either in isolation or accompanying more diffuse autoimmune encephalitic illnesses. The full range of movement phenomena has been described and, as they often occur in adults, many of the presentations can mimic neurodegenerative disorders, such as autoimmune chorea mimicking Huntington disease. Disorders may be ataxic, hypokinetic (parkinsonism), or hyperkinetic (myoclonus, chorea other dyskinetic disorders). The autoantibody targets are diverse and include neuronal surface proteins such as leucine-rich, glioma-inactivated 1 (LGII), as well as antibodies reactive with intracellular antigens (such as Purkinje cell cytoplasmic antibody-1: PCA-1) that are markers of a central nervous system process mediated by CD8+ cytotoxic T cells. In some instances (such as PCA-1 autoimmunity), antibodies detected in serum and cerebrospinal fluid can be indicative of a paraneoplastic cause, and may direct the cancer search. In other instances (such as 65kDa isoform of glutamic acid decarboxylase: GAD65 autoimmunity), a paraneoplastic cause is very unlikely, and early treatment with immunotherapy may promote improvement or recovery.

**Useful For:** Evaluating patients with suspected paraneoplastic or other autoimmune movement disorders including patients with ataxia, chorea, dyskinesias, myoclonus, parkinsonism, and stiff-person spectrum in serum specimens

**Interpretation:** A positive antibody result is consistent with a diagnosis of an autoimmune movement disorder. A search for cancer may be indicated, depending on the antibody profile. A trial of immune therapy may bring about improvement in neurological symptoms.

**Reference Values:**

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Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com
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<td>PCTBS</td>
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**Movement Disorder, Autoimmune Evaluation, Spinal Fluid**

**Clinical Information:** Autoimmune movement disorders encapsulate a large and diverse group of neurologic disorders occurring either in isolation or accompanying more diffuse autoimmune encephalitic illnesses. The full range of movement phenomena has been described and, as they often occur in adults, many of the presentations can mimic neurodegenerative disorders, such as autoimmune chorea mimicking Huntington disease. Disorders may be ataxic, hypokinetic (parkinsonism), or hyperkinetic (myoclonus, chorea other dyskinetic disorders). The autoantibody targets are diverse and include neuronal surface proteins such as leucine-rich, glioma-inactivated 1 (LGI1), as well as antibodies reactive with intracellular antigens (such as Purkinje cell cytoplasmic antibody-1: PCA-1) that are markers of a central nervous system process mediated by CD8+ cytotoxic T cells. In some instances (such as PCA-1 autoimmunity), antibodies detected in serum and cerebrospinal fluid can be indicative of a paraneoplastic cause, and may direct the cancer search. In other instances (such as 65 kDa isofrom of glutamic acid decarboxylase: GAD65 autoimmunity), a paraneoplastic cause is very unlikely, and early treatment with immunotherapy may promote improvement or recovery.

**Useful For:** Evaluating patients with suspected paraneoplastic or other autoimmune movement disorders including patients with ataxia, chorea, dyskinesias, myoclonus, parkinsonism, and stiff-person spectrum using spinal fluid specimens

**Interpretation:** A positive antibody result is consistent with a diagnosis of an autoimmune movement disorder. A search for cancer may be indicated, depending on the antibody profile. A trial of immune therapy may bring about improvement in neurological symptoms.

**Reference Values:**
<table>
<thead>
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<th>Reporting Name</th>
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<th>Reference Value</th>
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Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, CRMP-5-IgG, PCA-1, PCA-2, or PCA-Tr may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."


**MPL Exon 10 Mutation Detection, Reflex, Varies**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular...
signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder. Evaluates for mutations in MPL in an algorithmic process for the MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

**Interpretation:** An interpretation will be provided under the MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

**Reference Values:**
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

An interpretive report will be provided.

**MPL Exon 10 Mutation Detection, Varies**

**Clinical Information:** DNA sequence mutations in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocythemia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase and the most common MPL mutations are single base pair substitutions at codon 515. These mutations have been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 mutations have been identified in PMF and ET to date, and mutations outside of exon 10 have not yet been reported. The vast majority of MPL mutations have been found in specimens testing negative for the most common mutation identified in myeloproliferative neoplasms, JAK2 V716F, although a small number of cases with both types of mutations have been reported. MPL mutations have not been identified in patients with polycythemia vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL mutations can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm

**Interpretation:** The results will be reported as 1 of 2 states: -Negative for MPL exon 10 mutation -Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MPL Exon 10 Sequencing, Reflex, Varies**

**Clinical Information:** JAK2 V617F variant is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). Detection of the JAK2 V617F is useful to help establish the diagnosis of a myeloproliferative neoplasm (MPN). However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in
BCR-ABL1-negative MPN include CALR exon 9 alterations (20%-30% of PMF and ET) and MPL exon 10 alterations (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm when JAK2V617F testing result is negative Evaluates for variants in MPL in an algorithmic process for MPNCM / Myeloproliferative Neoplasm, CALR with Reflex to MPL, Varies.

**Interpretation:** The results will be reported as 1 of the 3 following states: -Positive for CALR variant -Positive for MPL variant -Negative for CALR and MPL variants Positive variant status is highly suggestive of a myeloid neoplasm and clinicopathologic correlation is necessary in all cases. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms.

**Reference Values:**
Only orderable as a reflex. For more information see MPNCM / Myeloproliferative Neoplasm, CALR with Reflex to MPL, Varies.

An interpretive report will be provided.

**Clinical References:**

**MSH2I**

**MSH-2, Immunostain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MSH6I**

**MSH-6, Immunostain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**MSH2Z**

**MSH2 Gene, Full Gene Analysis, Varies**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer: HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other Lynch
 syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are below 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious alterations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MSH2 and MSH6 are more likely to have a germline variant in the MSH2 gene.

**Useful For:** Determining whether absence of MSH2 protein, by immunohistochemistry in tumor tissue, is associated with a germline variant in the affected individual Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer Identification of familial MSH2 variant to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**MSH2 Immunostain, Technical Component Only**

**Clinical Information:** Hereditary nonpolyposis colorectal cancer (HNPPC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with
increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. Testing tumors from individuals at risk for Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by Lynch syndrome usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have Lynch syndrome or somatic hypermethylation of MLH1.

Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this Lynch syndrome screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. Â The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Â Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


MSH6 Gene, Full Gene Analysis, Varies

Clinical Information: Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer: HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious alterations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MSH6 are more likely to have a germline variant in the MSH6 gene.

Useful For: Determining whether absence of MSH6 protein, by immunohistochemistry in tumor tissue, is associated with a germline variant in the affected individual Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Clinical Information: Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. HNPCC is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated with MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the HNPCC spectrum. Several clinical variants of HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair phenotype within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this HNPCC screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

Useful For: Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the
context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CSMRT

mSMART Plasma Cell Proliferative Disorder, Pre-Analysis Cell Sorting, Bone Marrow

Clinical Information: Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow classifies patients into either standard or high-risk categories based on the results of 2 assays: plasma cell proliferation and FISH for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with multiple myeloma, which can assist in determining treatment and management decisions Sort plasma cells for FISH analysis Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

Reference Values: Only orderable as a reflex. See MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow

An interpretive report will be provided.


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MPCDS 606090

mSMART, Plasma Cell Proliferative Disorder, FISH, Bone Marrow

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell proliferative disorders (PCPD): monoclonal gammapathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over age 50 years, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders as a part of a profile Identifying prognostic markers based on the anomalies found

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

Reference Values:
Only orderable as part of a profile. For more information see MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow.

An interpretive report will be provided.


MTBVP

Mtb PZA Confirmation, pncA Sequencing (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MUCN2

Mucin 2, Immunostain, Technical Component Only

Clinical Information: Mucins are high molecular weight glycoproteins produced by epithelial cells and can be divided into 2 families. Mucin 2 (MUC2) is a 520 kDa glycoprotein belonging to the family of secretory mucins and is normally expressed in the cytoplasm of goblet cells. An immunopanel consisting of MUC1, MUC2, MUC5AC and MUC6 is useful in subtyping intraductal papillary mucinous neoplasms (IPMN).

Useful For: Aiding in subtyping intraductal papillary mucinous neoplasms (IPMN).

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


MUCN4

Mucin 4, Immunostain, Technical Component Only

Clinical Information: Mucin 4 (MUC4) is a large membrane-anchored glycoprotein that belongs to the mucin family. Mucins play important roles in the protection of epithelial cells and have been implicated in epithelial renewal and differentiation. MUC4 is expressed in the cytoplasm and membrane of respiratory, gastrointestinal, cervical, and prostatic epithelial cells. Overexpression of MUC4 has been observed in many carcinomas. It has been shown to be useful for the distinction between sarcomatoid carcinoma (often expressed) versus sarcomatoid mesothelioma (usually negative).

Useful For: Aids in the differentiation of sarcomatoid carcinoma from sarcomatoid mesothelioma
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**MUCN5**

### Mucin 5AC, Immunostain, Technical Component Only

**Clinical Information:** Mucins are high-molecular weight glycoproteins produced by epithelial cells and can be divided into 2 families. Mucin 5AC (MUC5AC) is a glycoprotein belonging to the family of secretory mucins and is expressed in the regenerative zone of gastric epithelium. An immunopanel consisting of MUC1, MUC2, MUC5AC and MUC6 is useful in subtyping intraductal papillary mucinous neoplasms (IPMN).

**Useful For:** Aiding in subtyping intraductal papillary mucinous neoplasms (IPMN)

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**MUCN6**

### Mucin 6, Immunostain, Technical Component Only

**Clinical Information:** Mucins are high-molecular weight glycoproteins produced by epithelial cells and can be divided into 2 families. Mucin 6 (MUC6) is a large glycoprotein that plays a major role in the protection of the gastrointestinal tract and belongs to the family of secretory mucins. MUC6 is expressed in the cytoplasm/membrane of gastric pyloric epithelial cells. An immunopanel consisting of MUC1, MUC2, MUC5AC and MUC6 is useful in subtyping intraductal papillary mucinous neoplasms (IPMN).

**Useful For:** Aiding in subtyping intraductal papillary mucinous neoplasms (IPMN)
**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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### Mucopolysaccharides Quantitative, Random, Urine

**Clinical Information:** The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin-6-sulfate, which are collectively called glycosaminoglycans (GAGs). Undegraded or partially degraded GAGs are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in mucopolysaccharidosis (MPS) disorders. There are 11 known enzyme deficiencies that result in the accumulation of mucopolysaccharides. In addition, abnormal glycosaminoglycan storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. Mucopolysaccharidoses are autosomal recessive disorders with the exception of MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood. A diagnostic workup for individuals with suspected MPS should begin with this test which includes the quantitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates, or GAGs. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the quantitative analysis of their amounts of excretion. However, an abnormal mucopolysaccharide analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) and/or molecular analysis. After a specific diagnosis has been established, this test can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy. This test allows for monitoring of the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment. Table: Enzyme Defects and Excretion Products of Mucopolysaccharidoses Disorder alias Enzyme Deficiency Sulfates Excreted MPS I Hurler/Scheie Alpha-L-iduronidase DS/HS MPS II Hunter Iduronate 2-sulfatase DS/HS MPS III A Sanfilippo A Heparan N-sulfatase HS MPS III B Sanfilippo B N-acetyl-alpha-D-glucosaminidase HS MPS III C Sanfilippo C Acetyl-CoA:alpha-glucosaminide N-acetyltransferase HS MPS III D Sanfilippo D N-acetylgalcosamine-6-sulfatase HS MPS IV A Morquio A Galactosamine-6-sulfatase KS/C6S MPS IV B Morquio B Beta-galactosidase KS MPS VI Maroteaux-Lamy Arylsulfatase B DS MPS VII Sly Beta-glucuronidase DS, HS, C6S MPS IX Hurler, Scheie Hurler, Scheie None KEY: C6S, chondroitin 6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate; MPS I (Hurler/Scheie syndrome) is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized.
into 3 main types: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which are not distinguishable via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months, with death occurring usually before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the third decade of life (20s). The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-galactosidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals. MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAG are normal in MPS IX.

**Useful For:** Supporting the biochemical diagnosis of one of the mucopolysaccharidoses: types I, II,
III, IV, VI, or VII

**Interpretation:** Elevations of dermatan sulfate and/or heparan sulfate and/or keratan sulfate and/or chondroitin-6-sulfate may be indicative of one of the mucopolysaccharidoses: types I, II, III, IV, VI, or VII. Elevations of any or all sulfate species may be indicative of multiple sulfatase deficiency or mucolipidosis II/III. Rarely, an elevation of keratan sulfate may be indicative of alpha-fucosidosis.

**Reference Values:**

**DERMATAN SULFATE**
< or = 1.00 mg/mmol creatinine

**HEPARAN SULFATE**
< or = 4 years: < or = 0.50 mg/mmol creatinine
> or = 5 years: < or = 0.25 mg/mmol creatinine

**CHONDROITIN-6 SULFATE**
< or = 24 months: < or = 10.00 mg/mmol creatinine
25 months-10 years: < or = 2.50 mg/mmol creatinine
> or = 11 years: < or = 1.50 mg/mmol creatinine

**KERATAN SULFATE**
< or = 12 months: < or = 2.00 mg/mmol creatinine
13-24 months: < or = 1.50 mg/mmol creatinine
25 months-4 years: < or = 1.00 mg/mmol creatinine
5-18 years: < or = 0.50 mg/mmol creatinine
> or = 19 years: < or = 0.30 mg/mmol creatinine

**Clinical References:**

**Mucopolysaccharides Quantitative, Serum**

**Clinical Information:** The mucopolysaccharidoses are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG, also called mucopolysaccharides). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in mucopolysaccharidosis (MPS) disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), and which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the
mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II (Hunter syndrome) is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the X-linked inheritance pattern, MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS-III (Sanfilippo syndrome) is caused by a reduced or absent activity of any 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAG especially dermatan sulfate, and can lead to death before the second or third decade of life. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAG, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase and is extremely rare. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. Elevations of dermatan sulfate and/or heparan sulfate are seen MPS types I, II, III, VI, and VII. Elevations of keratan sulfate are seen in MPS types IVA and IVB.

**Useful For:** Quantification of dermatan sulfate, heparan sulfate, and keratan sulfate in serum to support the biochemical diagnosis of one of the mucopolysaccharidoses types I, II, III, IV, VI, or VII.

**Interpretation:** Elevations of dermatan sulfate, heparan sulfate, and/or keratan sulfate may be indicative of one of the mucopolysaccharidoses types I, II, III, IV, VI, or VII. Elevations of all three sulfate species may be indicative of multiple sulfatase deficiency. Rarely, an elevation of keratan sulfate
may be indicative of alpha-fucosidosis.

**Reference Values:**

**DERMATAN SULFATE**  
< or =300.00 ng/mL

**HEPARAN SULFATE**  
< or =55.00 ng/mL

**TOTAL KERATAN SULFATE**  
< or =5 years: < or =1800.00 ng/mL  
6-18 years: < or =1500.00 ng/mL  
> or =19 years: < or =1200.00 ng/mL


**Mucopolysaccharidosis III, Multi-Gene Panel, Varies**

**Clinical Information:** Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the accumulation of heparan sulfate in various tissues. Sanfilippo syndrome A is caused by variants in SGSH and is characterized by reduced or absent activity of the sulfamidase enzyme. Sanfilippo syndrome B is caused by variants in NAGLU and is characterized by reduced or absent activity of the N-acetyl-alpha-D-glucosaminidase. Sanfilippo syndrome C is caused by variants in HGSNAT and is characterized by reduced or absent activity of the acetyl-CoA:alpha-glucosaminide N-acetyltransferase enzyme. Sanfilippo syndrome D is caused by variants in GNS and is characterized by reduced or absent activity of the N-acetylgalactosamine-6-sulfatase enzyme. Sanfilippo syndrome presents with a spectrum of central nervous system degeneration and physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Measurement of mucopolysaccharides in blood or urine can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot or MPSQU / Mucopolysaccharides Quantitative, Random, Urine).

**Useful For:** Identifying variants within the SGSH, NAGLU, HGSNAT, and GNS genes Confirmation of a diagnosis of mucopolysaccharidosis type III, also known as Sanfilippo syndrome

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**  
An interpretive report will be provided.

**Clinical References:** 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the
Mucopolysaccharidosis IIIA, Full Gene Analysis, Varies

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfatase. Mucopolysaccharidosis type IIIA (MPS-IIIA), or Sanfilippo syndrome A, is caused by variants in the SGSH gene and is characterized by reduced or absent activity of the sulfamidase enzyme. This test screens for variants in all 8 exons of the SGSH gene. Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20â€™s. Measurement of mucopolysaccharides in blood or urine can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot or MPSQU / Mucopolysaccharides Quantitative, Random, Urine).

Useful For: Identifying sequence variants within the SGSH gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIA Carrier testing, when there is a family history of mucopolysaccharidosis type IIIA, but disease-causing variants have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Mucopolysaccharidosis IIIB, Full Gene Analysis, Varies

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfatase. Mucopolysaccharidosis type IIIB (MPS-IIIB), or Sanfilippo syndrome B, is caused by variants in the NAGLU gene and is characterized by reduced or absent activity of the N-acetyl-alpha-D-glucosaminidase. This test screens for variants in all 6 exons of the NAGLU gene. Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20â€™s. Measurement of...
Mucopolysaccharidosis IIIC, Full Gene Analysis, Varies

**Clinical Information:** Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIIC (MPS-III-C), or Sanfilippo syndrome C, is caused by variants in the HGSNAT gene and is characterized by reduced or absent activity of the heparin acetyl-CoA:alpha-glucosaminide N-acetyltransferase enzyme. This test screens for variants in all 18 exons of the HGSNAT gene. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20â€™s.

**Useful For:** Identifying variants within the HGSNAT gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIC Carrier testing, when there is a family history of mucopolysaccharidosis type IIIC, but disease-causing variants have not been previously identified

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Mucopolysaccharidosis IIID, Full Gene Analysis, Varies**

**Clinical Information:** Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIID (MPS-IIID), or Sanfilippo syndrome D, is caused by variants in the GNS gene and is characterized by reduced or absent activity of the N-acetylglucosamine-6-sulfatase enzyme. This test screens for variants in all 14 exons of the GNS gene. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20â€™s. Measurement of mucopolysaccharides in blood or urine can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot or MPSQU / Mucopolysaccharides Quantitative, Random, Urine).

**Useful For:** Identifying variants within the GNS gene Confirmation of a diagnosis of mucopolysaccharidosis type IIID Carrier testing when there is a family history of mucopolysaccharidosis type IIID, but disease-causing variants have not been previously identified

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Mucopolysaccharidosis VI, Full Gene Analysis, Varies**

**Clinical Information:** Mucopolysaccharidosis type VI (MPS-VI), also known as Maroteaux-Lamy syndrome, is an autosomal recessive condition that is caused by variants in the ARSB gene and is characterized by reduced or absent activity of the arylsulfatase B enzyme. This test screens for variants in all 8 exons of the ARSB gene. The clinical features and severity of symptoms of Maroteaux-Lamy are widely variable. Typically it is characterized by short stature, dysostosis multiplex, facial dysmorphism, stiff joints, hepatosplenomegaly, corneal clouding, cardiac defects, and usually normal intelligence. With a rapidly progressing form of MPS-VI, onset occurs before 2 to 3 years of age with death typically occurring in the second to third decade. With a slowly progressing form of MPS-VI, a diagnosis usually occurs after 5 years of age but may not occur until the second or third decade. The recommended first-tier test for MPS-VI is measurement of mucopolysaccharides in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or enzyme testing for arylsulfatase B.

**Useful For:** Identifying variants within the ARSB gene Confirmation of a diagnosis of mucopolysaccharidosis type VI Carrier testing, when there is a family history of mucopolysaccharidosis type VI, but disease-causing variants have not been previously identified
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MPSWB 113435**

**Mucopolysaccharidosis, Blood**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG, also called mucopolysaccharides). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroGLOSSIA, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome, is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the x-linked inheritance pattern, MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS-III, Sanfilippo syndrome, is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. MPS-III is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most
commonly behavioral problems and delayed development, usually occurs between 2 and 6 years of age in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills with death generally occurring by their 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA, Morquio A syndrome, is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB, Morquio B syndrome, is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI; Maroteaux-Lamy syndrome, is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAG especially dermatan sulfate, and can lead to death before the second or third decade. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAG, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Elevations of dermatan or heparan sulfate are seen in MPS types I, II, III, and VI. Elevations of keratan sulfate are seen in MPS IV.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses type I, II, III, IV, or VI

Quantification of heparan sulfate, dermatan sulfate, and keratan sulfate in whole blood

Interpretation: Elevations of dermatan sulfate and/or heparan sulfate may be indicative of 1 of the mucopolysaccharidoses types I, II, III, or VI. Elevations of keratan sulfate may be indicative of mucopolysaccharidoses type IV.

Reference Values:

**DERMATAN SULFATE (DS)**
- Newborn-< or =2 weeks: < or =200 nmol/L
- >2 weeks: < or =130 nmol/L

**HEPARAN SULFATE (HS)**
- Newborn-< or =2 weeks: < or =96 nmol/L
- >2 weeks: < or =95 nmol/L

**TOTAL KERATAN SULFATE (KS)**
- < or =5 years: < or =1900 nmol/L
- 6-10 years: < or =1750 nmol/L
- 11-15 years: < or =1500 nmol/L
- >15 years: < or =750 nmol/L

Clinical References:
Mucopolysaccharidosis, Blood Spot

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs, also called mucopolysaccharides). Undegraded or partially degraded GAGs are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroGLOSSIA, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome, is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the x-linked inheritance pattern, MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS-III, Sanfilippo syndrome, is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years of age in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills with death generally occurring by their 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IV, Morquio A syndrome, is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB, Morquio B syndrome, is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of
MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI, Maroteaux-Lamy syndrome, is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAG especially dermatan sulfate, and can lead to death before the second or third decade. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAG, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Elevations of dermatan and/or heparan sulfate are seen in MPS types I, II, III, and VI. Elevations of keratan sulfate are seen in MPS IV.

**Useful For:** Supporting the biochemical diagnosis of mucopolysaccharidoses types I, II, III, IV, or VI

**Interpretation:** Elevations of dermatan sulfate and/or heparan sulfate may be indicative of 1 of the mucopolysaccharidoses: type I, II, III, or VI. Elevations of keratan sulfate may be indicative of mucopolysaccharidoses type IV.

**Reference Values:**

**DERMATAN SULFATE (DS)**
- Newborn (<2 weeks): <200 nmol/L
- >2 weeks: <130 nmol/L

**HEPARAN SULFATE (HS)**
- Newborn (<2 weeks): <96 nmol/L
- >2 weeks: <95 nmol/L

**TOTAL KERATAN SULFATE (KS)**
- <5 years: <1,900 nmol/L
- 6-10 years: <1,750 nmol/L
- 11-15 years: <1,500 nmol/L
- >15 years: <750 nmol/L

**Clinical References:**

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**Mucor, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing a diagnosis of an allergy to mucor Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>2</td>
<td>0.70-3.49</td>
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<td>5</td>
<td>50.0-99.9</td>
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<td>6</td>
<td>&gt; or =100</td>
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</tbody>
</table>

Reference values apply to all ages.


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**Mugwort, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to mugwort Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Mulberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mulberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0                 Negative
1 0.35-0.69  Equivocal
2 0.70-3.49  Positive
3 3.50-17.4   Positive
4 17.5-49.9  Strongly positive
5 50.0-99.9  Strongly positive
6 > or =100  Strongly positive Reference values apply to all ages.
Multiple Myeloma Gene Panel, Next-Generation Sequencing, Bone Marrow

Clinical Information: Multiple myeloma (MM) is a malignancy of bone marrow plasma cells with an annual incidence of 200,000 per annum. Comprehensive clinical, radiologic, and laboratory evaluation can initially stratify patients by disease phase and burden. Cytogenetic and FISH studies are important to help classify MM into standard, intermediate, and high risk groups. Advances in nontargeted therapies, including autologous bone marrow transplantation, have significantly improved the outcome of many patients; however, most patients with myeloma suffer relapse after initial treatment. Clinical next-generation sequencing (NGS) technology has enabled a deeper and more detailed evaluation of MM genetics. Testing allows for further risk categorization of the disease through the identification of additional abnormalities of prognostic and potentially therapeutic value. Application of targeted NGS-based analysis is a useful adjunct to the standard evaluation of MM patients at diagnosis and relapse. This test comprises a DNA-based multigene panel that includes preanalytic plasma cell enrichment, NGS, and detailed analysis resulted in a clinical report.

Useful For: Evaluation of multiple myeloma at the time of diagnosis, for prognostic and potential therapeutic indications Identification of the presence of new, clinically important, gene alteration changes at relapse

Interpretation: An interpretive report will be provided that includes the gene alterations identified, if present.

Reference Values:
An interpretive report will be provided.

Clinical References:

Multiple Myeloma Minimal Residual Disease by Flow, Bone Marrow

Clinical Information: Multiple myeloma is an incurable malignant neoplasm of plasma cells. One of the best prognostic factors in multiple myeloma is the level of minimal residual disease post chemotherapy or autologous stem cell transplantation. The greater depth of the response (less malignant cells present), the longer time to progression and overall survival.(1)

Useful For: Detection of low level (minimal residual disease) myeloma cells after therapy

Interpretation: The interpretation of the test is done by an evaluating automated and manually gated populations to isolate abnormal plasma cells. If there is an abnormal plasma cell population (cluster of 20 cells or more), then the result is minimal residual disease (MRD)-positive, with the percentage of abnormal plasma cells out of total analyzed events. If no abnormal population is found, then the result will be interpreted as MRD-negative.

Reference Values:
An interpretive report will be provided.
This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the previous patient history will be provided by a hematopathologist for every case.

**Clinical References:**

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**Multiple Myeloma Pre-Analysis Cell Sorting, Bone Marrow**

**Clinical Information:** Testing allows for further risk categorization of the multiple myeloma (MM) through the identification of additional abnormalities of prognostic and potentially therapeutic value. Application of targeted next-generation sequencing-based analysis is a useful adjunct to the standard evaluation of MM patients at diagnosis and relapse.

**Useful For:** Evaluation of multiple myeloma at the time of diagnosis, for prognostic and potential therapeutic indications

**Interpretation:** Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

**Reference Values:**
Only orderable as a reflex. For more information see NGSMM / NGSMM Multiple Myeloma Gene Panel, Next-Generation Sequencing, Bone Marrow.

**Clinical References:**

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**Multiple Sclerosis (MS) Profile, Serum and Spinal Fluid**

**Clinical Information:** Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease characterized by visual, motor, and sensory disturbances. The diagnosis of MS is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the kappa free light chains in cerebrospinal fluid (CSF) and CSF oligoclonal band detection.

**Useful For:** Diagnosing multiple sclerosis, especially helpful in patients with equivocal clinical or radiological findings

**Interpretation:** When result is 0.1000 mg/dL or more, the kappa free light chain concentration measured in cerebrospinal fluid (CSF) is at or greater than the threshold associated with demyelinating disease. This is a positive result. These findings, however, are not specific for multiple sclerosis (MS) because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic
diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). Clinical correlation is recommended. Automatic reflexing to oligoclonal bands will occur. When result is less than 0.0600 mg/dL, the kappa free light chain concentration measured in CSF is lower than the threshold associated with demyelinating disease. This is a negative result. Testing for oligoclonal banding is not performed. Clinical correlation is recommended. When result is 0.0600 to 0.0999 mg/dL, the kappa free light chain concentration measured in CSF is slightly elevated but not above the medical decision point of 0.1000 mg/dL associated with demyelinating disease. This is a borderline result. Reflexing to oligoclonal bands will be automatically performed and clinical correlation is recommended. When the oligoclonal band assay detects 2 or more unique IgG bands in the CSF, the result is positive. CSF is used in the diagnosis of MS by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria. These findings, however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation is recommended.

**Reference Values:**

KAPPA FREE LIGHT CHAIN  
Medical decision point: 0.1000 mg/dL

OLIGOCLONAL BANDS:  
<2 bands

**Clinical References:**  

**SUMFZ**

**Multiple Sulfatase Deficiency, Full Gene Analysis, Varies**

**Clinical Information:** Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal storage disorder (LSD) caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1 encodes for a formylglycine-generating enzyme (FGE) that performs a critical posttranslational modification of the catalytic residue necessary for activation of all human sulfatases. MSD is often confused for a single sulfatase deficiency because it is characterized by deficiency of all known sulfatases, which results in tissue accumulation of sulfatides, sulfated glycoaminoglycans, sphingolipids, and steroid sulfates. Indeed, the clinical phenotype encompasses symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy (MLD), the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Age of onset and clinical severity are variable and correspond with the level of residual FGE enzyme activity. A severe neonatal form of MSD closely overlaps the clinical presentation of the mucopolysaccharidoses but it is often fatal within 1 year. Late-infantile MSD (onset 0-2 years) accounts for most cases and is characterized by a clinical presentation similar to MLD. Patients show progressive cognitive and motor impairment as well as skeletal changes. More rarely, MSD presents in late childhood (juvenile-onset) with more mild symptoms and slower progression. Patients with late-infantile or juvenile-onset MSD may have less severe sulfatase deficiency. Patients with a clinical suspicion of MLD, a mucopolysaccharidosis, X-linked ichthyosis, or chondrodysplasia should be investigated for possible FGE deficiency. Urine sulfatide analysis is the recommended first tier biochemical test (CTSA / Ceramide Trihexoside/Sulfatide Accumulation in Urine Sediment, Urine). If positive, iduronate sulfatase and aroylsulfatase A and B enzyme levels should be assayed and are typically decreased in patients with MSD. While enzyme replacement therapy has been used to treat a subset of
single LSD, its effectiveness is not well established for patients with MSD. Therefore, confirmation or exclusion of a diagnosis of MSD has important implications for patient management as well as prognosis.

**Useful For:** Confirmation of multiple sulfatase deficiency for patients with clinical features
Identification of SUMF1 mutation to allow for genetic testing in family members

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MUM1B**

**MUM-1/IRF4 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** MUM-1 (multiple myeloma oncogene-1), expressed by the IRF4 gene, is seen in a subset of B cells in the light zone of the germinal center (representing late stages of B cell differentiation), plasma cells, activated T cells, and a variety of hematolymphoid neoplasms derived from these cells. Among non-hematolymphoid neoplasms, MUM-1 expression has been reported in melanomas. A separate protocol optimized for B5 fixed/decalcified bone marrow specimens has been validated.

**Useful For:** Aiding in the identification of hematolymphoid neoplasms and melanomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**MUM1**

**MUM-1/IRF4 Immunostain, Technical Component Only**

**Clinical Information:** MUM-1 (multiple myeloma oncogene-1), expressed by the IRF4 gene, is seen in a subset of B cells in the light zone of the germinal center (representing late stages of B cell differentiation), plasma cells, activated T cells, and a variety of hematolymphoid neoplasms derived...
from these cells. Among non-hematolymphoid neoplasms, MUM-1 expression has been reported in melanomas. A separate protocol optimized for B5 fixed/decalcified bone marrow specimens has been validated.

**Useful For:** Aids in the identification of hematolymphoid neoplasms and melanomas

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CMUMP**

**Mumps Virus Antibodies, IgG and IgM, Spinal Fluid**

**Clinical Information:** There is only one serotype of mumps virus that infects humans. Mumps has been recognized since antiquity by virtue of the parotitis, which is often a striking clinical feature of the disease. Generally, a trivial childhood illness, the varied presentation of mumps reflects the widespread invasion of visceral organs and central nervous system that commonly follows infection with mumps virus.

**Useful For:** Aiding in the diagnosis of central nervous system infection by mumps virus

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

**Reference Values:**
- IgG: <1:5
- IgM: <1:10
  
  Reference values apply to all ages.

**Clinical References:**

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**MPPG**

**Mumps Virus Antibody, IgG, Serum**

**Clinical Information:** The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus (RSV), and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2 week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise. Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5%
of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction (PCR) in throat, saliva, or urine specimens.

**Useful For:** Determination of postimmunization immune response of individuals to the mumps vaccine Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

**Interpretation:** Positive: The presence of detectable IgG-class antibodies indicates prior exposure to the mumps virus through infection or immunization. Individuals testing positive are considered immune to mumps virus. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies suggests no prior exposure to the mumps virus or the lack of a specific immune response to immunization.

**Reference Values:**
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

**Clinical References:**

---

**Mumps Virus Antibody, IgM and IgG, Serum**

**Clinical Information:** The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1–4, measles, respiratory syncytial virus, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximate 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(1,2) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction in throat, saliva, or urine specimens.

**Useful For:** Diagnosis of mumps virus infection Determination of postimmunization immune response of individuals to the mumps vaccine Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

**Interpretation:** A positive IgG result coupled with a positive IgM result suggests recent infection with mumps virus. This result should not be used alone to diagnose mumps infection and should be
interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with mumps virus. These individuals are considered to have protective immunity to re-infection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to mumps virus and nonimmunity. However, a negative result does not rule out mumps infection or response to vaccination. The specimen may have been collected before the appearance of detectable antibodies. Negative results in suspected early mumps infection or within a week following vaccination should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

**Reference Values:**

IgM:
- Negative
  - Index value 0.00-0.79 = negative
- Reference values apply to all ages.

IgG:
- Vaccinated: Positive (> or = 1.1 AI)
- Unvaccinated: Negative (< or = 0.8 AI)
- Reference values apply to all ages.

**Clinical References:**
Murine Typhus Antibodies, IgG

Clinical Information: A fourfold increase in antibody titer between acute and convalescent specimens is consistent with recent infection. A single titer $\geq 1:128$ can be consistent with recent infection. Titters of $1:16$ to $1:64$ can be indicative of recent or past infection.

Useful For: Detect antibodies following infection with murine typhus.

Reference Values:
Reference Interval:
- Negative: $<1:64$
- Present or Past: $1:64$
- Recent/Active: $>1:64$

Muscle Pathology Consultation

Clinical Information: This consultative practice strives to bring the customer the highest quality of diagnostic neuromuscular pathology, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

Useful For: Obtaining a rapid, expert opinion on muscle biopsy specimens for neuromuscular disease

Interpretation: Results are reported in a formal neuromuscular pathology report that includes diagnosis and an interpretive comment, if necessary. The formal pathology report is faxed or sent by mail according to the preference of the referring institution.

Reference Values:
An interpretive report will be provided.

Clinical References:
neuromuscular junction is characteristic of myasthenia gravis (MG). The diagnosis is made by clinical and electromyographic criteria. Positive autoimmune serology must be interpreted in the clinical and electrophysiological context and response to anticholinesterase medication. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic acetylcholine receptor or its interacting proteins).(1) Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (71% muscle acetylcholine receptor: AChR binding).(2) Mayo Clinic Laboratories' first-line serological evaluation detects muscle AChR antibody in 92% of nonimmunosuppressed patients with generalized weakness due to MG. Muscle-specific kinase (MuSK) antibody is detectable in more than one-third of those seronegative for muscle AChR antibody (less than 4% of all patients).(3) Physiologically, MuSK is involved in integrating and stabilizing AChR clusters in the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Antibodies to LRP4 itself have been described in rare patients.(1) Six percent of nonimmunosuppressed patients with generalized MG lack demonstrable AChR or MuSK antibodies (double seronegative). Other rare autoantibodies no doubt remain to be discovered in such cases. However, as in autoimmune AChR MG and MuSK MG, testing for common organ-specific and nonorgan-specific autoantibodies is a valuable ancillary investigation in evaluating seronegative acquired generalized MG. General serological testing, coupled with family or personal history, will disclose autoimmune phenomena in 77% of those cases.(3) These disorders may include thyroid disease, type 1 diabetes, vitiligo, premature greying, rheumatoid arthritis, or lupus. Testing may also reveal antinuclear antibodies, glutamic acid decarboxylase (GAD65) antibodies, thyroperoxidase/thyroglobulin antibodies, or gastric parietal cell antibodies.(3) Objective improvement in strength following a therapeutic trial of plasmapheresis or intravenous immune globulin would justify consideration of long-term immunosuppression. Females are generally affected by autoimmune MuSK MG more often than males. Onset can occur at any age (pediatric to elderly). Patients may derive limited benefit from anticholinesterase medication. The thymus is normal, and patients are generally not benefited by thymectomy. Antibody-lowering therapies are effective. Bulbar, facial, and respiratory weakness are prominent, and crises are common.(1,4)

**Useful For:** Diagnosis of autoimmune muscle-specific kinase (MuSK) myasthenia gravis Second-order test to aid in the diagnosis of autoimmune myasthenia gravis when first-line serologic tests are negative Establishing a quantitative baseline value for MuSK antibodies that allows comparison with future levels if weakness is worsening

**Interpretation:** A positive result, in the appropriate clinical context, confirms the diagnosis of autoimmune muscle-specific kinase myasthenia gravis. Seropositivity justifies consideration of immunotherapy.

**Reference Values:**
< or =0.02 nmol/L


**Mushroom IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.
This test should only be ordered by physicians who recognize the limitations of the test.

**MUSH 82626**

**Mushroom, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to mushroom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Reference Values apply to all ages.**


**FMTFG 57679**

**Mustard Food IgG**

**Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to...
select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**MSTD**

82801

**Mustard, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to mustard Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
| 6     | > or =100| Strongly positive Reference values apply to all ages.


**MYHZ**

65603

**MUTYH Gene, Full Gene Analysis, Varies**

**Clinical Information:** Biallelic germline mutations in the MUTYH gene (also known as MYH) cause MUTYH-associated polyposis (MAP) syndrome, an autosomal recessive form of hereditary colorectal cancer. MAP is a polyposis syndrome typically associated with 10 to 100 adenomatous colon polyps, which in turn confer a significantly increased risk for colorectal cancer. Therefore, phenotypic overlap exists between MAP and attenuated familial adenomatous polyposis (FAP). However, the number of
cumulative polyps is variable and can mimic both classic FAP, associated with hundreds to thousands of polyps, and Lynch syndrome, which is generally associated with very few (1-5) adenomatous polyps. Therefore, evaluation for MUTYH should be considered in patients with early onset colorectal cancer in whom a DNA mismatch repair (MMR) defect has not been identified. Patients with biallelic MUTYH mutations are at risk for extracolonic manifestations including upper gastrointestinal polyps or cancer as well as other tumors. Congenital hyperpigmentation of the retinal epithelium (CHRPE), dental anomalies, dermal cysts, desmoid tumors, and osteomas may also occur, but to a lesser extent than what is observed in patients with FAP. Literature suggests that monoallelic carriers may also be at increased risk for colon, gastric, breast, and endometrial cancer. Approximately 1% to 2% of mixed European Caucasian individuals are predicted to carry a MUTYH mutation. Therefore, the reproductive partners of monoallelic and biallelic carriers should be offered carrier screening to adequately assess the risk of their offspring to have MAP. Two mutations, G396D and Y179C (originally known as G382D and Y165C), account for approximately 85% of the disease-causing MUTYH mutations in affected mixed European Caucasian individuals.

**Useful For:** Confirmation of suspected clinical diagnosis of MUTYH-associated polyposis (MAP) in patients with adenomatous polyps or early-onset colorectal cancer Identification of familial MUTYH mutations to allow for predictive or diagnostic testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
cross-reactive anti-CCD IgE antibodies, although the presence of IgE antibodies to profilin proteins should also be considered. The degree to which antibodies to CCD may be associated with clinical allergic reaction has not been completely resolved. In general, the presence of cross-reactive antibodies to CCD, such as MUXF3, is not thought to be clinically relevant and does not give rise to symptoms consistent with allergic reaction. However, antibodies to CCD may be linked to clinically relevant allergic reactions in extremely rare cases, including in individuals with celery and tomato allergy.

**Useful For:** Evaluation for the presence of antibodies to cross-reactive carbohydrate determinates (CCD) Investigation of clinically unexpected positive IgE antibody testing in a wide variety of plant and invertebrate allergens

**Interpretation:** Antibody to bromelain MUXF3 has widely been used for assessing for potential cross-reactive carbohydrate determinate (CCD) cross-reactivity since its CCD chain is also found in many other plant proteins, including peanuts. While sensitization to CCD is generally not associated with an allergic reaction, the presence of IgE antibodies to CCD may give rise to confounding positive IgE antibody sensitization profiles for a wide variety of plant and invertebrate allergens.

**Reference Values:**

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<td>Negative</td>
</tr>
<tr>
<td>0.10-0.34</td>
<td>0/1</td>
<td>Borderline/Equivocal</td>
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<tr>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>0.70-3.49</td>
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</tr>
<tr>
<td>3.50-17.4</td>
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<td>Positive</td>
</tr>
<tr>
<td>17.5-49.9</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>50.0-99.9</td>
<td>5</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>6</td>
<td>Strongly positive Concentrations &gt; or =0.70 kU/L (Class 2 and above) will flag as abnormally high.</td>
</tr>
</tbody>
</table>

**Clinical References:**

**FBMO 75510**

**MVista Blastomyces Quantitative Antigen, Fluid**

**Reference Values:**
- Reference Value: None Detected
- Results reported as ng/mL in 0.2 - 14.7 ng/mL range
- Results above the limit of detection but below 0.2 ng/mL are reported as 'Positive, Below the Limit of Quantification'
- Results above 14.7 ng/mL are reported as 'Positive, Above the Limit of Quantification'
**FBMS**

75509

**MVista Blastomyces Quantitative Antigen, Serum**

**Reference Values:**
Reference Interval: None Detected
- Results reported as ng/mL in 0.2 - 14.7 ng/mL range
- Results above the limit of detection but below 0.2 ng/mL are reported as 'Positive, Below the Limit of Quantification'
- Results above 14.7 ng/mL are reported as 'Positive, Above the Limit of Quantification'

**FMVCO**

57122

**MVista Coccidioides Antigen EIA**

**Reference Values:**
Reference Interval: None Detected
- Results reported as ng/mL in 0.07 - 8.2 ng/mL range
- Results above 8.2 ng/mL are reported as 'Positive, Above the Limit of Quantification'

**FHST**

91957

**MVista Histoplasma Ag Quantitative EIA**

**Reference Values:**
Reference Interval: None Detected
- Reportable Range: Positive Results reported in ng/mL from 0.20 ng/mL to 20.00 ng/mL
- Positive Results above 20.00 ng/mL are reported as 'Positive, Above the Limit of Quantification'

**FHOST**

90018

**MVista Histoplasma Ag Quantitative, Serum**

**Reference Values:**
Reference Interval: None Detected
- Reportable Range: Positive Results reported in ng/mL from 0.20 ng/mL to 20.00 ng/mL
- Positive Results above 20.00 ng/mL are reported as 'Positive, Above the Limit of Quantification'

**FHSAG**

90017

**MVista Histoplasma Ag Quantitative, Spinal Fluid**

**Reference Values:**
Reference Interval: None Detected
- Reportable Range: Positive Results reported in ng/mL from 0.20 ng/mL to 20.00 ng/mL
- Positive Results above 20.00 ng/mL are reported as 'Positive, Above the Limit of Quantification'

**MGMR**

608980

**Myasthenia Gravis Evaluation with Muscle-Specific Kinase (MuSK) Reflex, Serum**

**Clinical Information:** Fatigable weakness due to impaired postsynaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). A clinical diagnosis should be supported by electrodiagnostic testing, ie, clinical-electrodiagnosis (EDX). Positive autoimmune serology increases certainty of MG diagnosis but needs to be interpreted in the proper clinical-EDX context with response to anticholinesterase medications supporting the diagnosis. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules.
(nicotinic muscle acetylcholine receptor [AChR] or its interacting proteins, such as muscle-specific kinase [MuSK]). Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (72% are positive for AChR binding antibodies) and highest in patients with generalized weakness due to MG (92% are positive for AChR binding antibodies). In adults with MG and AChR antibodies, approximately 20% will have thymoma and, very rarely (<1%), extrathymic cancers.

Computerized tomography (CT) imaging of the chest is considered the standard of care to evaluate for thymoma. MuSK antibody is detectable in more than one-third of patients with MG and are seronegative for muscle AChR antibodies. MuSK is involved in integrating and stabilizing AChR clusters at the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Patients with MuSK MG are more commonly female. Onset can occur at any age (pediatric to older adult). Patients derive less benefit from anticholinesterase medications and no neoplasm has associated with MuSK MG. Although beneficial, thymectomy has not been demonstrated to be helpful in MuSK MG. Patients with both AChR and MuSK autoantibodies benefit from immunotherapy, however, patients with MuSK autoantibodies tend to have more steroid dependence. In patients with seronegative MG, reconsideration of the diagnosis is important. If clinical-EDX criteria are still met, repeating serological testing within one year can increase serological positivity for AChR antibodies by 15%. The diagnostic sensitivity of these tests depends on the disease severity and duration of symptoms. AChR binding antibodies may be undetectable for 6 to 12 months after MG symptom onset. Only about 5% of adult patients with generalized MG who at not immunosuppressed remain seronegative for muscle AChR beyond 12 months. Objective improvement by electrodiagnostic and strength testing following a therapeutic trial of plasmapheresis or intravenous immune globulin can justify consideration of long-term immunosuppression in patients who are seronegative meeting clinical-EDX criteria. Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

**Useful For:** Diagnosis for autoimmune myasthenia gravis (MG) in adults and children Distinguishing autoimmune from congenital MG in adults and children or other acquired forms of neuromuscular junction transmission disorders Establishing a quantitative baseline value that allows comparison with future levels if weakness is worsening

**Interpretation:** Positive results in this antibody evaluation are indicative of autoimmune myasthenia gravis (MG). These results should be interpreted in the appropriate clinical and electrophysiological context. In the presence of either acetylcholine receptor (AChR) antibodies a paraneoplastic basis should be considered with thymoma being the most commonly associated tumor with myasthenia gravis. Currently, muscle-specific kinase (MuSK) antibody positive MG is not associated with a paraneoplastic etiology. Negative results do not exclude the diagnosis of an autoimmune neuromuscular junction disorder. If clinical suspicion remains and symptoms persistent or worsen consider re-testing.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Methodology</th>
<th>Reference Value</th>
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<tbody>
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<td>MGMRI MG with MuSK Interpretation, S</td>
<td>Interpretation</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ARBI ACh Receptor (Muscle) Binding Ab</td>
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<tr>
<td>ACMFS AChR Modulating Flow Cytometry, S</td>
<td>Flow Cytometry</td>
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<tr>
<td>MUSK MuSK Autoantibody, S</td>
<td>RIA</td>
<td>&lt; or =0.02 nmol/L</td>
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</tbody>
</table>


### Myasthenia Gravis/Lambert-Eaton Myasthenic Syndrome Evaluation, Serum

**Clinical Information:** Myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) are acquired autoimmune disorders of neuromuscular transmission. MG is caused by pathogenic autoantibodies binding and potentially removing (modulation) the muscle’s nicotinic acetylcholine receptor (AChR) from the surface of the neuromuscular junction. Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. A subset of patients who are AChR seronegative will have muscle-specific kinase (MuSK) antibodies. LEMS is caused by autoantibodies binding to motor nerve terminal’s voltage-gated P/Q-type calcium channel. Synaptic transmission fails when autoantibodies cause a critical loss of junctional cation channel proteins that activate the muscle action potential. Both MG and LEMS can affect children as well as adults, although LEMS is very rare in children. In adults MG is 10 times more frequent than LEMS, but it is sometimes difficult to distinguish the two disorders clinically. Electrophysiological testing is extremely helpful in distinguishing these 2 disorders. MG patients have decrements of compound muscle action potential (CMAP) amplitudes on repetitive stimulation whereas LEMS has immediate and dramatic post exercise facilitation (elevation) of CMAP amplitudes. Neoplasms associated with LEMS or MG are an endogenous source of the antigens driving production of the autoantibodies that characterize each disorder. In adults with MG, there is at least a 20% occurrence of thymoma and, very rarely (<1%), extrathymic cancers. LEMS is frequently associated (80%) with small-cell lung carcinoma (SCLC). Thus far, MuSK antibody associated MG has not been associated with any neoplasm. The diagnostic sensitivity of these tests depends on the disease severity and duration of symptoms. AChR binding antibodies may be undetectable for 6 to 12 months after MG symptom onset and similarly P/Q-type calcium channel antibody may be undetectable for 6 to 12 months after LEMS onset. Only about 5% of adult patients with generalized MG who are not immunosuppressed remain seronegative for muscle AChR beyond 12 months. Although immunotherapy is universally beneficial for MG, in LEMS resection of the identified SCLC and initiation of 3-4 diaminopyridine, which facilitates acetylcholine release by increasing presynaptic calcium concentration, is most beneficial. Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

**Useful For:** Confirming the autoimmune basis of a defect in neuromuscular transmission (e.g., myasthenia gravis [MG], Lambert-Eaton myasthenic syndrome [LEMS]) Distinguishing LEMS from autoimmune forms of MG Providing a quantitative autoantibody baseline for future comparisons in monitoring a patient’s clinical course and response to immunomodulatory treatment

**Interpretation:** Positive results in this antibody evaluation are indicative of an autoimmune neuromuscular junction disorder. These results should be interpreted in the appropriate clinical and electrophysiological context. In the presence of either acetylcholine receptor (AChR) antibodies or P/Q antibodies, a paraneoplastic basis should be considered with thymoma being the most commonly associated tumor with myasthenia gravis and small cell lung cancer being the most commonly associated cancer with Lambert-Eaton myasthenic syndrome. Currently, muscle-specific kinase (MuSK) antibody positive myasthenia gravis (MG) is not associated with a paraneoplastic etiology. Negative results do not exclude the diagnosis of an autoimmune neuromuscular junction disorder. If clinical suspicion remains and symptoms persistent or worsen consider re-testing.

**Reference Values:**

<table>
<thead>
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<th>Test ID</th>
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<td>608979</td>
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</tbody>
</table>

**SGTF**

**MYB (6q23) Rearrangement FISH, Tissue**

**Clinical Information:** Salivary adenoid cystic carcinomas (ACC), although uncommon, are frequent among salivary gland malignancies. ACC is typically an aggressive tumor with a poor prognosis. Histologically, ACC show significant morphologic overlap with other salivary gland tumors, but have a much different clinical course. Because ACC requires a management distinct from histologically similar lesions, it is important to make an accurate diagnosis. Translocations between MYB (6q23.3) and NFIB (9p24) have been identified in a large proportion of primary salivary gland ACC. These alterations have not been identified in other salivary gland tumors. Therefore, separation of MYB, in the proper clinical and histologic context, is diagnostic for ACC and can be confirmed by FISH with MYB break-apart probes.

**Useful For:** Assessing for MYB gene rearrangements in patients with primary salivary gland carcinoma to aid in confirming or excluding the diagnosis of primary salivary gland adenoid cystic carcinomas

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the MYB locus. The presence of a MYB rearrangement in conjunction with the proper clinical and histologic features is diagnostic of adenoid cystic carcinomas (ACC). A confirmed diagnosis of ACC results in specific clinical management that may be distinct from the management of other salivary gland neoplasms. A negative result suggests no rearrangement of the MYB gene region at 6q23.3. The absence of a MYB rearrangement does not exclude the diagnosis of ACC, as a subset of ACCs do not show an MYB rearrangement.

**Reference Values:**
An interpretive report will be provided.

MYC Immunostain, Technical Component Only

Clinical Information: MYC is a proto-oncogene commonly overexpressed in many malignant neoplasms, including some B-cell lymphomas. MYC translocations are a hallmark abnormality of Burkitt lymphoma. The presence of the MYC translocation may be a helpful indicator of poor prognosis or an aggressive clinical course in diffuse large B-cell lymphoma.

Useful For: Assessment of MYC expression

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Mycobacteria and Nocardia Culture, Varies

Clinical Information: Mycobacteria species are responsible for significant morbidity and mortality in both immunocompromised and immunocompetent hosts. Mycobacterium tuberculosis is the causative agent of tuberculosis, and it kills nearly 2 million people in the world each year. Nontuberculous mycobacteria such as Mycobacterium avium complex and Mycobacterium abscessus cause a variety of infections (eg, respiratory, skin, and soft tissue) and are important to detect and correctly identify in order to aid in clinical decision making. There are approximately 200 recognized species of mycobacteria and identification of these organisms to the species level is often required to help guide appropriate therapy. Although there are direct detection methods available for M tuberculosis, growth of the organism on culture media is still necessary to allow for antimicrobial susceptibility testing. At this time, direct molecular detection methods are lacking for the nontuberculous mycobacteria and growth in culture is critical for identification and antimicrobial susceptibility testing. Nocardia species and other aerobic actinomycetes (eg, Tsukamurella species, Gordonia species, Rhodococcus species) are also important causes of disease and isolation on culture media is important to facilitate identification and antimicrobial susceptibility testing. Nocardia and the other aerobic actinomycetes grow well on mycobacterial medium, and therefore, ordering a mycobacterial culture is recommended when infection with this group of organisms is suspected.

Useful For: Detection and identification of Mycobacterium species, Nocardia species, and other aerobic actinomycetes Identification is performed using the Hologic/GenProbe AccuProbes for selected Mycobacterium species, matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, or 500-base pair 16S rRNA gene sequencing Mycobacterium tuberculosis complex species identification can be done upon request using rapid polymerase chain-reaction (PCR) targeting the regions of difference (RD) genomic areas

Interpretation: A final negative report is issued after 42 days of incubation. Positive cultures are reported as soon as detected.

Reference Values: Negative

Clinical References: 1. Pyffer GE, Palicova F: Mycobacterium: general characteristics;

**ISMY**

**Mycobacteria Ident by Sequencing (Bill Only)**

**Reference Values:**
This test is for billing purposes only. This is not an orderable test.

**TBPB**

**Mycobacteria Probe Ident Broth (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**TBMP**

**Mycobacteria Probe Ident Solid (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**CTBBL**

**Mycobacterial Culture, Blood**

**Clinical Information:** Mycobacteremia occurs most often in immunocompromised hosts. The majority of disseminated mycobacterial infections are due to Mycobacterium avium complex but bacteremia can also be caused by other mycobacterial species including, but not limited to, Mycobacterium tuberculosis complex, Mycobacterium kansasii, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium scrofulaceum, Mycobacterium szulgai, and Mycobacterium xenopi. (1) Mycobacterial blood cultures may be indicated for patients presenting with signs and symptoms of sepsis, especially fever of unknown origin.

**Useful For:** Diagnosing mycobacteremia

**Interpretation:** A positive result may support the diagnosis of mycobacteremia.

**Reference Values:**
Negative
If positive, mycobacteria is identified.
A final negative report will be issued after 42 days of incubation.


**TBSP**

**Mycobacterium tuberculosis Complex Species Identification, PCR, Varies**

**Clinical Information:** This assay provides a species-level identification of microbiologic culture isolates previously identified to be a member of the Mycobacterium tuberculosis complex. Species level identification can be important for patient care or for epidemiologic investigations. For example, the
species-level identification of Mycobacterium bovis bacillus Calmette-Guerin (BCG) can assist with identification of disseminated infections following use of the vaccine as an adjuvant during chemotherapy.

**Useful For:** Determining the species of a Mycobacterium tuberculosis complex culture isolate

**Interpretation:** This assay can differentiate the most common species within the Mycobacterium tuberculosis complex, which are, M tuberculosis, Mycobacterium bovis, Mycobacterium bovis bacillus Calmette-Guerin (BCG; the vaccine strain), Mycobacterium canetti, Mycobacterium caprae, Mycobacterium microti, and Mycobacterium pinnepedi. This assay cannot distinguish Mycobacterium africanum from Mycobacterium mungi so if that result is obtained, the organism will be reported as M africanum/M mungi.

**Reference Values:**
Not applicable

**Clinical References:** Fitzgerald DW, Sterling TR, Haas DW: Mycobacterium tuberculosis. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2985-3021

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**Mycobacterium tuberculosis Complex, Molecular Detection of Drug Resistance Markers, Whole Genome Sequencing, Varies**

**Clinical Information:** An important component of disease management for patients with tuberculosis is testing of Mycobacterium tuberculosis complex isolates for resistance to first- and second-line antituberculous medications. Phenotypic culture-based drug resistance testing is often performed using broth methods since they are more rapid than the gold-standard agar proportion method. However, even the rapid broth methods require approximately 14 days culture and identification of the isolate as M tuberculosis complex before susceptibility testing can be performed. This whole genome sequencing (WGS) testing provides molecular detection of well-characterized drug-resistance variants in M tuberculosis complex by sequencing M tuberculosis isolates. It is intended to aid in the detection of resistance to first- and second-line antituberculous agents including isoniazid, rifampin, ethambutol, pyrazinamide, the fluoroquinolones (moxifloxacin and ofloxacin) and the aminoglycosides (streptomycin, kanamycin, and amikacin). This testing evaluates selected genes of interest including: Drug/Drug Class Gene Isoniazid ahpC fabG1 inhA katG Rifampin rpoB Ethambutol embB Pyrazinamide pncA Fluoroquinolones gyrA Aminoglycosides eis gidB rpsL rrs

**Useful For:** Molecular detection of drug resistance variants in culture isolates of the Mycobacterium tuberculosis complex May provide a more rapid detection of drug resistance than phenotypic, broth-based testing Aiding in the resolution of discrepant results obtained using phenotypic methods testing for M tuberculosis isolates that are not sufficiently viable to allow for culture-based testing

**Interpretation:** Variants detected in the queried genes of Mycobacterium tuberculosis complex that are highly associated with drug resistance are reported along with an indication of how often the detected gene variant correlated with phenotypic culture-based drug resistance in a verification study of the whole genome sequencing method. For example, detection of an rpoB S450L variant would be reported as "rpoB S450L" and a comment would be included on the report stating "probable rifampin resistance; in a study of 173 isolates, 35/35 (100%) of isolates with this variant were resistant to rifampin." If no variants associated with drug resistance are detected in the M tuberculosis complex isolate, a "no variant detected" result is reported along with an indication of how often isolates in the verification study that displayed phenotypic culture-based drug resistance had a variant in the evaluated gene. For example, if no variant was detected in the gyrA gene, the report would indicate "No variant detected" and a comment stating "In a study of 173 isolates, 22/23 (95.7%) of fluoroquinolone resistant isolates had a variant in gyrA." Genetic variants of unknown significance are not reported.

**Reference Values:**
Results are reported as variant detected or no variant detected.

**Clinical References:** 1. Kozyreva VK, Truong C-L, Greninger AL, Crandall J, Mukhopadhyay R,

Mycobacterium tuberculosis Complex, Molecular Detection, PCR, Paraffin, Tissue

Clinical Information: Each year, Mycobacterium tuberculosis accounts for approximately 1.4 million deaths and is responsible for 9 million newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person-to-person via respiratory transmission, and has the potential to become resistant to many or all of the antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid PCR assay detects M tuberculosis complex DNA directly from respiratory specimens and other specimens without waiting for growth in culture and, therefore, the results are available the same day the specimen is received in the laboratory. A mycobacterial culture should always be performed in addition to the PCR assay. This assay is rapid but the culture has increased sensitivity over it. The PCR assay targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex. In addition, the assay can detect genotypic resistance to isoniazid mediated by variants in the katG target, when present.

Useful For: Preferred method for rapid detection of Mycobacterium tuberculosis complex DNA in formalin-fixed, paraffin-embedded tissue specimens Detection of M tuberculosis complex The PCR assay is not intended for the detection of latent tuberculosis and must not be used as a substitute for tests intended for detection of latent tuberculosis such as the tuberculin skin test (TST/PPD) or an interferon gamma release assay (IGRA).

Interpretation: A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. Members of the M tuberculosis complex detected by this assay include M tuberculosis, M bovis, M bovis bacillus Calmette-Guerin (BCG), M africanum, M canettii, and M microti. The other species within the M tuberculosis complex (eg, M caprae, M pinnipedi, and M mungi) should, in theory, be detected using the primer and probe sequences in this assay, but they have not been tested at this time. This assay method does not distinguish between the species of the M tuberculosis complex. A negative result indicates the absence of detectable M tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG variant will be reported when observed but lack of a katG variant does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug. An inhibition result indicates that inhibitors are present in the specimen that could prevent the detection of M tuberculosis DNA. A new specimen can be resubmitted under a new order, if desired.

Reference Values:
Not applicable

**Clinical Information:** Mycobacterium tuberculosis is a highly transmissible bacterial pathogen and is the causative agent of tuberculosis, a disease causing significant worldwide morbidity and mortality. Each year, M tuberculosis accounts for nearly 1.3 million deaths and is responsible for 10 million newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person to person via respiratory transmission, and has the potential to become resistant to many of the antibiotics currently used if not treated appropriately. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 6 weeks of incubation may be required in some instances. This qualitative molecular assay utilizes PCR-based nucleic acid amplification for the direct detection of M tuberculosis DNA within respiratory specimens without relying on culture growth, leading to more rapid diagnoses and appropriate patient care. This assay also detects the presence of mutations in the rpoB gene that have been documented to confer more than 95% of cases of rifampin resistance.

**Useful For:** Rapid detection of Mycobacterium tuberculosis DNA from respiratory specimens for the diagnosis of pulmonary tuberculosis. Presumptive detection of rifampin resistance based on the presence of resistance-associated mutations.

**Interpretation:** A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. A negative result indicates the absence of detectable M tuberculosis complex DNA. Presumptive rifampin (RIF) resistance mediated through mutations within the resistance determining region of the rpoB gene will be reported when detected. One to 2 negative PCR results in conjunction with 1 to 2 negative acid-fast smears may provide evidence supporting the removal of a patient from airborne isolation. Consult your local Infection Prevention and Control for guidance.

**Reference Values:**
- Negative

**Clinical References:**

**MTBRP 88807**

**Mycobacterium tuberculosis Complex, Molecular Detection, PCR, Varies**

**Clinical Information:** Each year, Mycobacterium tuberculosis accounts for approximately 1.4 million deaths and is responsible for 9 million newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person-to-person via respiratory transmission, and has the potential to become resistant to many or all of the antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid PCR assay detects M tuberculosis complex DNA directly from respiratory specimens and other specimens without waiting for growth in culture and, therefore, the results are available the same day the specimen is received in the laboratory. A mycobacterial culture should always be performed in addition to the PCR assay. The PCR assay is rapid but the culture has increased sensitivity over the PCR assay. The PCR assay targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex. In addition, the assay can detect genotypic resistance to isoniazid mediated by mutations in the katG target, when present.

**Useful For:** Rapid detection of Mycobacterium tuberculosis complex DNA, preferred method.
Detection of M. tuberculosis, when used in conjunction with mycobacterial culture. This test should not be used to determine bacteriologic cure or to monitor response to therapy. This test is not intended for the detection of latent tuberculosis and must not be used as a substitute for tests intended for detection of latent tuberculosis such as the tuberculin skin test (TST/PPD) or an interferon gamma release assay (IGRA).

**Interpretation:** A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. Members of the M. tuberculosis complex detected by this assay include M. tuberculosis, M. bovis, M. bovis bacillus Calmette-Guerin (BCG), M. africanum, M. canetti, and M. microti. Other species within the M. tuberculosis complex (e.g., M. caprae, M. pinnipedii, and M. mungi) should, in theory, be detected using the primer and probe sequences in this assay, but they have not been tested. This assay method does not distinguish between the species of the M. tuberculosis complex. A negative result indicates the absence of detectable M. tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG variant will be reported when observed but lack of a katG variant does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug.

**Reference Values:**
Not applicable

**Clinical References:**

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**MTBpZ 56099**

**Mycobacterium tuberculosis Complex, Pyrazinamide Resistance by pncA DNA Sequencing, Varies**

**Clinical Information:** The protein product of the Mycobacterium tuberculosis complex pncA gene is an enzyme that is responsible for activation of the prodrug pyrazinamide (PZA). DNA sequencing of the Mycobacterium tuberculosis complex pncA gene can be used to detect mutations that correlate with in vitro PZA resistance. The sequencing result can be available in as little as 1 day after the Mycobacterium tuberculosis complex isolate grows in culture, thereby providing a more rapid susceptibility result than the average 10 to 14 days required by phenotypic broth methods.

**Useful For:** Detection of genotypic resistance to pyrazinamide by Mycobacterium tuberculosis complex isolates

**Interpretation:** Polymorphisms in the pncA gene that have been previously correlated in our laboratory with pyrazinamide (PZA) resistance will be reported as "Mutation was detected in pncA suggesting resistance to pyrazinamide." Wild-type pncA or a silent pncA gene polymorphism (i.e., no change in the amino acid translation) will be reported as "No mutation was detected in pncA." New polymorphisms in the pncA gene that have not previously been seen in our laboratory will require additional testing using a reference broth method to determine their correlation with PZA resistance.

**Reference Values:**
Pyrazinamide resistance not detected

**Clinical References:**
Mycophenolic Acid, Serum

Clinical Information: Mycophenolate mofetil (CellCept) is a new immunosuppressive agent useful in organ transplantation. It is approved for use in renal, hepatic, and cardiac transplants. When mycophenolate mofetil enters the blood, it is immediately metabolized to the active drug, mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase and interferes with the de novo pathway of guanosine nucleotide synthesis selectively in lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. MPA acts in the same fashion as azathioprine, and MPA is suggested as replacement therapy for azathioprine. The drug is deactivated by the hepatic enzyme, uridine diphosphate glucuronosyltransferase to form mycophenolic acid glucuronide (MPA-G). The principle clinical problem encountered in MPA therapy is excessive immunosuppression, which predisposes the patient to systemic infection. Measurement of the blood level of MPA and MPA-G can be useful to guide therapy. Monitoring is recommended immediately after transplant up to 3 weeks after therapy is initiated to evaluate dosing adequacy. Additional monitoring is indicated if the MPA level is not in the therapeutic range or if a major change in health status occurs.

Useful For: Monitoring therapy to ensure adequate blood levels and avoid over-immunosuppression

Interpretation: Trough serum levels of mycophenolic acid (MPA) at steady-state (>2 weeks at the same dose) in the range of 1.0 to 3.5 mcg/mL indicate adequate therapy. Mycophenolic acid glucuronide (MPA-G) levels in the range of 35 to 100 mcg/mL indicate that the patient has normal uridine diphosphate glucuronosyltransferase (UGT) metabolic capacity. MPA-G levels are typically in the range of 100 to 250 mcg/mL during the 2 weeks following transplantation. MPA-G typically decreases after this initial post-transplant phase. Trough steady-state serum MPA levels over 4.0 mcg/mL indicate that the patient is over-immunosuppressed and susceptible to systemic infections. Decreased dosages may be indicated in these cases. Low MPA levels and high MPA-G levels suggest that the patient has an active UGT metabolic capability; higher doses may be required to maintain therapeutic levels of MPA. Some patients have a high UGT metabolic capacity. These patients may require 1 gram or more 3 times a day to maintain trough serum MPA levels in the range of 1.0 mcg/mL to 3.5 mcg/mL. They are likely to have MPA-G levels over 100 mcg/mL. MPA-G is inactive; MPA-G levels only describe the patient's metabolic status. Patients who have low UGT conjugating capability may become over-immunosuppressed, indicated by a trough steady-state serum MPA level over 4.0 mcg/mL and a MPA-G level below 40 mcg/mL. Dose reduction or interval prolongation is indicated in this case.

Reference Values:
MYCOPHENOLIC ACID (MPA)
1.0-3.5 mcg/mL

MPA GLUCURONIDE
35-100 mcg/mL


Mycoplasma hominis, Molecular Detection, PCR, Plasma

Clinical Information: Mycoplasma hominis has been associated with a number of clinically significant infections, although it is also part of the normal genital flora. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may occur without specific treatment, in premature infants, clinical manifestations of meningoencephalitis have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum infections.
fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extranatal infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity. In lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of M hominis infection in lung transplant recipients.

**Useful For:** Rapid, sensitive, and specific identification of Mycoplasma hominis from plasma

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Mycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum**

**Clinical Information:** Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community-acquired pneumonia. Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited, although severe disease has been reported in immunocompromised patients. Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology-based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week and the IgM response in adults may be variable or it may be decreased in immunosuppressed individuals. Confirmation of the disease is dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing. Real-time PCR offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens allows for diagnosis of acute or current infection.

**Useful For:** Screening for recent or past exposure to Mycoplasma pneumoniae This test should not be used as a screening procedure for the general population.

**Interpretation:** IgG ELISA Result IgM ELISA Result Interpretation Positive Negative Results suggest past exposure. Positive Reactive Prior exposure to Mycoplasma pneumoniae detected. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Negative Negative No antibodies to M pneumoniae detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection.Â If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Reactive No prior exposure to Mycoplasma pneumoniae. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Equivocal Negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Reactive Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal ELISA = Enzyme-linked immunosorbent assay
Reference Values:
IgG: negative
IgM: negative
IgM by IFA: negative

Clinical References: 1. Smith T: Mycoplasma pneumoniae infections: diagnosis based on
RS, Simberkoff MS, Leaf HL: Mycoplasma pneumoniae and atypical pneumonia. In Bennett JE, Dolin
R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th
ed. Elsevier; 2020:2332-2339

MYCOG 48317
Mycoplasma pneumoniae Antibodies, IgG, Serum

Clinical Information: Mycoplasma pneumoniae is an important respiratory tract pathogen. Several
syndromes have been associated with the infection including pharyngitis, tracheobronchitis, pneumonia,
and inflammation of the tympanic membrane presenting as bulous myringitis. M pneumoniae accounts
for approximately 20% of all cases of pneumonia. Classically, it causes a disease that has been
described as primary atypical pneumonia. The disease is of insidious onset with fever, headache, and
malaise for 2 to 4 days before the onset of respiratory symptoms. Most cases do not require
hospitalization. Symptomatic infections attributable to this organism most commonly occur in children
and young adults (ages 2-19 years).

Useful For: Screen for recent or past exposure to Mycoplasma pneumoniae

Interpretation: A single positive IgG result only indicates previous immunologic exposure.
Negative results do not rule out the presence of acute or ongoing Mycoplasma pneumoniae-associated
disease. The specimen may have been drawn before the appearance of detectable antibodies. If testing is
performed too early following primary infection, IgG may not be detectable. If a Mycoplasma infection
is clinically suspected, a second, convalescent specimen should be submitted in 14 to 21 days.

Reference Values:
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae
Antibodies, IgG and IgM, Serum.

Negative

Clinical References: Smith T: Mycoplasma pneumoniae infections: diagnosis based on

MYCOM 48318
Mycoplasma pneumoniae Antibodies, IgM, Serum

Clinical Information: Mycoplasma pneumoniae is an important respiratory tract pathogen. Several
syndromes have been associated with the infection including pharyngitis, tracheobronchitis, pneumonia,
and inflammation of the tympanic membrane presenting as bulous myringitis. M pneumoniae accounts
for approximately 20% of all cases of pneumonia. Classically, it causes a disease that has been
described as primary atypical pneumonia. The disease is of insidious onset with fever, headache, and
malaise for 2 to 4 days before the onset of respiratory symptoms. Most cases do not require
hospitalization. Symptomatic infections attributable to this organism most commonly occur in children
and young adults (ages 2-19 years).

Useful For: Screen for recent or past exposure to Mycoplasma pneumoniae

Interpretation: Positive IgM results are consistent with recent infection, although false-positives
may occur (see Cautions). Negative results do not rule out the presence of acute or ongoing
Mycoplasma pneumoniae-associated disease. The specimen may have been drawn before the
appearance of detectable antibodies. If testing is performed too early following primary infection, IgM
may not be detectable. If a Mycoplasma infection is clinically suspected, a second, convalescent
specimen should be submitted in 14 to 21 days.
**Reference Values:**
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

**Negative**

**Clinical References:** Smith T: Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc 1986;61:830-831

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**MYCON 48319**

**Mycoplasma pneumoniae Antibody Interpretation**

**Reference Values:**
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

**MGRP 60755**

**Mycoplasmoides genitalium, Molecular Detection, PCR, Varies**

**Clinical Information:** Mycoplasmoides genitalium, formerly Mycoplasma genitalium, causes acute and chronic nongonococcal urethritis, cervicitis, and pelvic inflammatory disease. Culture isolation is technically challenging; polymerase chain reaction (PCR) is the diagnostic test of choice.

**Useful For:** Rapid, sensitive, and specific identification of Mycoplasmoides genitalium from genitourinary and reproductive sources This test is not intended for medicolegal use.

**Interpretation:** A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Mycoplasmoides genitalium tuf gene indicates the presence of M genitalium DNA in the specimen. A negative PCR result indicates the absence of detectable M genitalium DNA in the specimen, it but does not rule-out infection as false-negative results may occur due to the following; inhibition of PCR, sequence variability underlying the primers or probes, or the presence of M genitalium in quantities below the limit of detection of the assay.

**Reference Values:**
Not applicable


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**MPRP 62394**

**Mycoplasmoides pneumoniae, Molecular Detection, PCR, Varies**

**Clinical Information:** Mycoplasmoides pneumoniae, previously Mycoplasma pneumoniae, is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community acquired pneumonia.(1) Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited although severe disease has been reported in immunocompromised patients.(2) Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week and the IgM response in adults may be variable or it may be decreased in immunosuppressed individuals.(3,4) Confirmation of the disease may be dependent on the observation of
a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing.(4) Real-time polymerase chain reaction testing offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens.

Useful For: Diagnosis of infections due to Mycoplasma pneumoniae

Interpretation: A positive result indicates the presence of Mycoplasma pneumoniae. A negative result does not rule out the presence of M pneumoniae and may be due to the presence of inhibitors within the specimen matrix, or the presence of organisms at numbers below the limits of detection of the assay.

Reference Values: Not applicable


MYD88 Reflex to CXCR4 Mutation Detection, Varies

Clinical Information: Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma that is characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes and spleen. It is a B-cell neoplasm that can exhibit excess production of serum immunoglobulin-M symptoms related to hyper viscosity, tissue filtration, and autoimmune-related pathology. CXCR4 mutations are identified in approximately 30% to 40% of LPL/WM and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 mutations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib: A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients, a MYD88-L265P/CXCR4-WT (wild type) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients, and the MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 mutation. This test is used to aid in the prognostication and therapeutic management of LPL/WM.

Useful For: The prognostication and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

Interpretation: Mutations detected or not detected. An interpretive report will be issued under the LPLFX / Reflexive Testing of MYD88 and CXCR4.

Reference Values: Only orderable as a reflex. For more information, see LPLFX / Reflexive Testing of MYD88 and CXCR4

MYD88, L265P, Somatic Gene Mutation, DNA Allele-Specific PCR, Varies

Clinical Information: The single point alteration in MYD88, L265P, is present in 67% to 100% of patients with lymphoplasmacytic lymphoma, and these patients typically have clinical manifestations of Waldenstrom macroglobulinemia (often designated LPL/WM).

Useful For: Establishing the diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia Helping to distinguish lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (low-grade B-cell lymphoma) from other subtypes

Interpretation: Variant present or not detected; an interpretive report will be issued.

Reference Values:
Variant present or absent based on expected alteration polymerase chain reaction product size. Concurrent amplification of wild type MYD88 fragment determined for sample amplification integrity. MYD88 gene (NCBI accession NM_002468.4).

MAG-SGPG Ab (IgM), EIA

Reference Range:
< or = 1:1600

MAG Ab (IgM), EIA

<1:1600

Reference ranges for MAG IgM Antibody:
Normal: <1:1600
Moderately Elevated: 1:1600-1:3200
Highly Elevated: >=1:6400

Myelin Oligodendrocyte Glycoprotein (MOG-IgG1)
Fluorescence-Activated Cell Sorting (FACS) Assay, Serum

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease (IDD) that predominantly affects optic nerves and spinal cord. (1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD). (1-3) Brain lesions are observed in more than 60% of patients with NMOSD and approximately 10% will be MS-like. (4) Children tend to have greater brain involvement than adults, and brain lesions are more symptomatic than is typical for adult patients. (3) The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Some patients may present with acute disseminated encephalomyelitis (ADEM). Many patients with NMOSD are misdiagnosed as having MS. More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Approximately 80% of patients with NMO are seropositive for aquaporin-4 (AQP4)-IgG. (5-7) In the remaining 20% of patients, myelin oligodendrocyte glycoprotein (MOG)-IgG is detected in up to a third. (8) The pathogenic target for the remaining patients remains unknown. Detection of MOG-IgG is diagnostic of central nervous system (CNS) inflammatory demyelination, where the clinical phenotype (NMOSD, optic neuritis, transverse myelitis, ADEM) may be similar, but the immunopathology (astrocytopathy vs oligodendrogliopathy) and clinical outcome (worse vs better) is different. (9) Detection of MOG-IgG also predicts relapse. (10) More importantly, however, is that MOG-IgG seropositive IDDs are distinct from MS and treated differently. (8, 9) Treatments for IDDs seropositive for MOG-IgG include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Disease modifying agents, treatments promoted for MS, have been reported to exacerbate MOG-IgG1 seropositive IDDs. Therefore, early diagnosis and initiation of appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. In 2015, Waters and colleagues (11) from Oxford University established a novel cell based assay for the measurement of IgG1 MOG antibodies based on previous findings that MOG antibodies are almost exclusively of the IgG1 subclass. They showed that their MOG-IgG1 flow cytometry assay eliminated false positives without losing true positives with low titers. The detection of MOG-IgG1 allowed non MS demyelinating diseases (ADEM, AQP4-IgG negative neuromyelitis optica spectrum disorder: including ON, TM) to be distinguished from MS. (12) Using a similar assay to our MOG-IgG1 flow cytometry assay, demonstrated high specificity of their MOG-IgG1 assay in which 49 patients with MS, 13 healthy control sera, and 37 AQP4-seropositive serum samples were all negative at a dilution of 1:20. Of 58 patients fulfilling 2006 Wingerchuk criteria for NMO, 21 (36%) tested negative for AQP4-IgG MOG-IgG1 was detected by cell based assay in 8 (38%) of these cases. (13) Testing of 1,109 consecutive sera sent for AQP4-IgG testing, (12) revealed 40 AQP4-IgG and 65 MOG-IgG1 positive cases. None were positive for both. The clinical diagnoses obtained in 33 MOG-IgG1 positive patients included 4 NMO, 1 ADEM and 11 optic neuritis (n = 11). All 7 patients with probable MS were MOG-IgG1 negative. This study provides Class II evidence that the presence of serum MOG-IgG1 distinguishes non-MS central nervous system (CNS) demyelinating disorders from MS (sensitivity 24%, 95% confidence interval [CI] 9%-45%; specificity 100%, 95% CI 88%-100%). The assay validated here, was developed using the MOG construct.
provided by Dr. Waters (11) and the validation was based on a blinded comparison with the Oxford assay. Comparison was also made with the Euroimmun fixed cell based kit assay. (14) A recent longitudinal analysis with 2 year follow-up suggested that persistence of MOG-IgG is associated with relapses thus warranting relapse preventing. (10) Detection of MOG-IgG1 allows distinction from MS and is generally indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack in some, thereby reducing attack frequency and disability in the future.

**Useful For:** Diagnosis of inflammatory demyelinating diseases (IDD) with similar phenotype to neuromyelitis optica spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis Diagnosis of autoimmune myelin oligodendrocyte glycoprotein (MOG)-opathy Diagnosis of neuromyelitis optica (NMO) Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease Diagnosis of ADEM Prediction of a relapsing disease course

**Interpretation:** A positive value for myelin oligodendrocyte glycoprotein (MOG)-IgG is consistent with an neuromyelitis optica (NMO)-like phenotype, and in the setting of acute disseminated encephalomyelitis (ADEM), optic neuritis and transverse myelitis indicates an autoimmune oligodendrogliopathy with potential for relapsing course. Identification of MOG-IgG allows distinction from MS and may justify initiation of appropriate immunosuppressive therapy (not MS disease-modifying agents) at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months as persistence of MOG-IgG seropositivity predicts a relapsing course. This autoantibody is not found in healthy subjects.

**Reference Values:**
Negative


**Myelodysplastic Syndrome (MDS), FISH, Varies**

**Clinical Information:** Myelodysplastic syndromes (MDS) primarily occur in the older adult population and have a yearly incidence of 30 in 100,000 in persons older than 70 years of age. These disorders are typically associated with a hypercellular bone marrow and low peripheral blood counts, and with significant morbidity and mortality. The eventual clinical outcome for patients with MDS relates to...
either bone marrow failure or transformation to acute myeloid leukemia. MDS can be either primary (de novo) or secondary (due to previous treatment with alkylating or etoposide chemotherapy, with or without radiation). Cytogenetic studies can provide confirmatory evidence of clonality in MDS and can be used to provide clinical prognostic or diagnostic information. Clonal cytogenetic abnormalities are more frequently observed in cases of secondary MDS (80% of patients) than in primary MDS (40%–60% of patients). The common chromosomal abnormalities associated with MDS include: inv(3), -5/5q-, -7/7q-, +8, and 20q-. These abnormalities can be observed singly or in concert. In addition, MLL (KMT2A) rearrangements, t(1;3), and t(3;21) are more frequently associated with secondary MDS. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in MDS; however, some of the subtle rearrangements associated with secondary MDS can be missed (eg, MLL abnormalities).

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myelodysplastic syndromes or other myeloid malignancies Evaluating specimens in which standard cytogenetic analysis is unsuccessful Identifying and tracking known chromosome abnormalities in patients with myeloid malignancies and tracking response to therapy

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Myelodysplastic Syndrome by Flow Cytometry, Bone Marrow**

**Clinical Information:** Myelodysplastic syndromes (MDS) encompass a heterogeneous group of clonal hematopoietic neoplasms characterized by cytopenias due to ineffective hematopoiesis, variable degrees of dysmyelopoietic morphologic features, and increased risks of evolution to acute myeloid leukemia. Per 2008 World Health Organization recommendations, a definitive diagnosis of MDS requires identification of 1 or more of the following findings: clear-cut morphologic features of dysplasia in greater than or equal to 10% of the cells in 1 or more of the 3 hematopoietic lineages; increased (but <20%) blood or marrow blasts with or without Auer rods; and well-characterized clonal cytogenetic abnormalities.(3-4) However, at present, in approximately 50% of MDS patients, no informative or diagnostic clonal cytogenetic abnormalities are identified. Not infrequently, morphologic review of the patient’s blood and marrow specimen is inconclusive. And yet it is important to distinguish MDS and other clonal myeloid neoplasms from other nonmalignant and nonneoplastic possibilities in the differential diagnosis such as medication effects or other toxic exposures, copper deficiency, infections, and left-shifted hematopoietic regeneration, among others. In such settings, when used in conjunction with appropriate clinical and morphologic findings, flow cytometry immunophenotyping analysis can provide additional diagnostic information to help distinguish an underlying clonal hematopoietic neoplasm from a reactive or secondary response.(2,5)

**Useful For:** Detecting increased blasts Characterizing blast phenotypes Identifying abnormal patterns of myeloid maturation as seen in myelodysplastic syndromes and other clonal myeloid neoplasms Providing additional adjunct diagnostic information in cases with equivocal or suspicious morphologic features for myelodysplastic syndrome (MDS), MDS/myeloproliferative neoplasms including chronic myelomonocytic leukemia, and other clonal myeloid neoplasms.
**Interpretation:** The final interpretation integrates 1) the quantity of blasts; 2) blast phenotype with respect to CD13/HLA-DR expression and/or abnormal coexpression of CD2, CD7, and/or CD56; and 3) myeloid maturation patterns based on CD13/CD16 plot. In combination, the total number of abnormalities detected and the distinctiveness of the abnormalities themselves help determine the likelihood of specimen involvement by a clonal myeloid neoplasm.

**Reference Values:**
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

**Clinical References:**

**MSTF 35844**

**Myeloid Sarcoma, FISH, Tissue**

**Clinical Information:** Myeloid sarcomas are tumors made up of myeloblasts or immature myeloid cells that occur in extramedullary sites or in bone. They can occur concurrently with acute or chronic myeloid leukemia (AML or CML) or may precede the leukemia or other myeloid neoplasms. They may also be the initial manifestation of relapse of a previously treated primary AML in remission. Due to this extramedullary presentation, the bone marrow may have a low number of myeloblasts due to a lack of bone marrow involvement. The most common abnormalities seen in myeloid sarcomas are fusion of RUNX1T1/RUNX1 ([t(8:21)(q22;q22)], PML/RARA ([t(15;17)(q24;q21)], BCR/ABL1 ([t(9;22)(q34;q11.2)], inversion of MYH11/CBFB (inv[16](q13.1q22)), and rearrangements of MLL (KMT2A; [t(11q23;var)]. In general, AML patients with an inv(16), t(8;21), t(9;22), or t(15;17) have a favorable prognosis, while AML patients with a rearrangement of t(11q23) have an unfavorable prognosis. Thus, the detection of these abnormalities in an extramedullary presentation of AML can be prognostically important.

**Useful For:** Supporting the diagnosis of myeloid sarcoma when coordinated with a surgical pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a myeloid sarcoma. A negative result does not exclude the diagnosis of a myeloid sarcoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Myeloma, FISH, Fixed Cells

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell proliferative disorders (PCPD): monoclonal gammopathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over 50 years of age, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness, or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders Identifying prognostic markers based on the abnormalities found This test should not be used to track the progression of disease.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

Reference Values: An interpretive report will be provided.

Clinical References:

Myeloperoxidase (MPO) Immunostain, Technical Component Only

Clinical Information: Myeloperoxidase shows strong cytoplasmic immunoreactivity in neutrophilic and eosinophilic granulocytes and their precursors. Virtually all other cell types are negative for myeloperoxidase staining. Antibodies to myeloperoxidase are most useful diagnostically to support myeloid lineage in acute leukemias. These antibodies also facilitate the detection of granulocyte precursors in myeloproliferative disorders and myelodysplastic syndromes.
Useful For: A marker of myeloid lineage

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Myeloperoxidase Antibodies, IgG, Serum

Clinical Information: Myeloperoxidase (MPO) enzyme is found in neutrophil primary granules and monocyte lysosomes. MPO catalyzes the conversion of hydrogen peroxide to hypochlorite and hypochlorous acid. MPO is encoded by a single gene that undergoes posttranslational modification to produce the active enzyme found in leukocytes. Autoantibodies to MPO (MPO antineutrophil cytoplasmic antibodies: ANCA) occur in several diseases and may be involved in the pathogenesis of vascular inflammation in patients with microscopic polyangiitis (MPA).(1,2) Patients with MPA often develop MPO ANCA and may present with azotemia secondary to glomerulonephritis (pauci-immune necrotizing glomerulonephritis). MPO ANCA are not specific for MPA, and also may be detected in patients with systemic lupus erythematosus with or without lupus nephritis, Goodpasture syndrome and Churg-Strauss syndrome. Lupus nephritis and Goodpasture syndrome, as well as Wegener granulomatosis may present with azotemia and progressive renal failure. It is not possible to distinguish among these diseases on the basis of clinical signs and symptoms; autoantibody testing may be helpful.

Useful For: Evaluating patients suspected of having immune-mediated vasculitis, especially microscopic polyangiitis (MPA), when used in conjunction with other autoantibody tests (see Cautions) May be useful to follow treatment response or to monitor disease activity in patients with MPA

Interpretation: A positive result has a high predictive value for microscopic polyangiitis (MPA) in patients with negative test results for systemic lupus erythematosus (antinuclear antibodies) and Goodpasture syndrome (glomerular basement membrane antibody). A negative result significantly diminishes the likelihood that a patient has MPA.(3) While myeloperoxidase levels often decline following successful treatment of MPA, specific guidelines for this clinical purpose are not available.

Reference Values:
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.

Myeloproliferative Neoplasm, CALR with Reflex to MPL, Varies

**Clinical Information:** JAK2 V617F variant is present in 95% to 98% of polycythemia vera (PV) patients, 50% to 60% of primary myelofibrosis (PMF) patients, and 50% to 60% of essential thrombocythemia (ET) patients. Detection of the JAK2 V617F variant helps establish the diagnosis of a myeloproliferative neoplasm (MPN). However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variants (20%-30% of PMF and ET) and MPL exon 10 variants (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm when JAK2 V617F testing result is negative

**Interpretation:** The results will be reported as 1 of the 3 following states: -Positive for CALR variant -Positive for MPL variant -Negative for CALR and MPL variants Positive variants status is highly suggestive of a myeloid neoplasm and clinicopathologic correlation is necessary in all cases. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other
important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluating for variants in JAK2, CALR, and MPL genes in an algorithmic process

**Interpretation:** The results will be reported as 1 of the 4 following states: -Positive for JAK2 V617F variant -Positive for CALR variant -Positive for MPL variant -Negative for JAK2 V617F, CALR, and MPL variants Positive variant status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Myocarditis/Pericarditis Panel**

**Reference Values:**
MYOCARDITIS-PERICARDITIS PANEL

**COXSACKIE B(1-6) ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- ≥ 1:8 Antibody Detected

Single titers of > or = 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to
the CLIA regulations and is used for clinical purposes.

**ECHOVIRUS ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- > or = 1:8 Antibody Detected

Single titers > or = 1:32 are indicative of recent infection. Titers of 1:8 and 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

**INFLUENZA TYPES A AND B ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- > or = 1:8 Antibody Detected

Single titers of > or = 1:64 are indicative of recent infection. Titers of 1:8 to 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

**CHLAMYDOPHILA PNEUMONIAE ANTIBODIES (IgG, IgA, IgM)**

**REFERENCE RANGE:**
- IgG <1:64
- IgA <1:16
- IgM <1:10

The immunofluorescent detection of specific antibodies to Chlamyphila pneumoniae may be complicated by cross-reactive antibodies, non-specific antibody stimulation, or past exposure to similar organisms such as C. psittaci and Chlamydia trachomatis. IgM titers of 1:10 or greater usually indicate recent infection, and any IgG titer may indicate past exposure. IgA is typically present at low titers during primary infection, but may be elevated in recurrent exposures or in chronic infection.

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**MYOD1**

**Myogenic Differentiation Antigen 1 (MYOD1) Immunostain, Technical Component Only**

**Clinical Information:** Myogenic differentiation antigen 1 (MyoD1) is a myogenic nuclear regulatory protein that is normally expressed during embryogenesis. Nuclear expression of MyoD1 is restricted to myoblasts of developing skeletal muscle tissue. MyoD1 is present in the majority of rhabdomyosarcomas.
**MYOGE**

**Myogenin Immunostain, Technical Component Only**

**Clinical Information:** Myogenin is a member of a family of myogenic regulatory genes that include MyoD, myf5, and MRF4. These genes encode a set of transcription factors that are essential for muscle development. Expression of myogenin is restricted to cells showing skeletal muscle differentiation. Myogenin is found in the majority of rhabdomyosarcomas and Wilms tumors, and is absent in Ewing sarcoma and mature skeletal muscle.

**Useful For:** Marker of skeletal muscle differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**MYOGL**

**Myoglobin Immunostain, Technical Component Only**

**Clinical Information:** Myoglobin is found in skeletal and cardiac muscle, but not in smooth muscle, and functions as an oxygen transporting pigment. Antibodies to myoglobin may be useful in the diagnosis of rhabdomyosarcomas, but the proportion of positive cells may be small, and they may be distributed unevenly in the section. Staining for myoglobin is not seen in carcinomas or other sarcomas.

**Useful For:** Marker of skeletal muscle differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Useful For:** Marker of skeletal and cardiac muscle

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**MYGLU**

**Myoglobin, Random, Urine**

**Clinical Information:** Myoglobin is the oxygen-binding protein of striated muscle. Injury to skeletal or cardiac muscle results in the release of myoglobin. High concentrations appear very rapidly in the urine in various conditions including some metabolic diseases. Conditions associated with myoglobinuria include: -Hereditary myoglobinuria -Phosphorylase deficiency -Sporadic myoglobinuria -Exertional myoglobinuria in untrained individuals -Crush syndrome -Myocardial infarction -Myoglobinuria of progressive muscle disease -Heat injury Urine myoglobin increases with muscle necrosis, but the clinical consequences are variable. Therefore, myoglobin can confirm a clinical diagnosis of myopathy, but an elevated urine excretion of myoglobin is not specific for a clinical disorder. In acute renal failure, an elevated urinary myoglobin can suggest a potential cause and, consequently, may indicate appropriate treatment courses.

**Useful For:** Confirming the presence of a myopathy associated with any 1 of the following disorders -Hereditary myoglobinuria -Phosphorylase deficiency -Sporadic myoglobinuria -Exertional myoglobinuria in untrained individuals -Crush syndrome -Myocardial infarction -Myoglobinuria of progressive muscle disease -Heat injury May suggest a myopathic cause for acute renal failure

**Interpretation:** Increased excretion of urinary myoglobin is suggestive of 1 of the following disorders: -Hereditary myoglobinuria -Phosphorylase deficiency -Sporadic myoglobinuria -Exertional myoglobinuria in untrained individuals -Crush syndrome -Myocardial infarction -Myoglobinuria of progressive muscle disease -Heat injury Most clinically significant elevations are elevated 2 to 10 times normal. Visual pigmenturia occurs at myoglobin concentrations about 200 times normal (approximately 4000 mcg/L). Renal toxicity depends on multiple factors such as renal perfusion and degree of acidity of urine.

**Reference Values:**
- < or =65 mcg/L for 18-83 years of age
- Reference values have not been established for patients<18 or >83 years of age.


**MYGLS**

**Myoglobin, Serum**

**Clinical Information:** Myoglobin is a heme protein found in smooth and skeletal muscles. Serum myoglobin reflects a balance between intravascular release of myoglobin from muscle and renal...
clearance. Previously serum myoglobin had been advocated as a sensitive marker for early acute myocardial injury (eg, acute myocardial infarction: AMI). However, more recent studies indicate that other newer markers (eg, troponin) provide superior diagnostic utility in detecting early myocardial injury. Elevation of serum myoglobin may occur as a result of muscle trauma, resuscitation, myopathies, AMI, shock, strenuous body activity, or decreased elimination during renal insufficiency. Extreme elevations occur in rhabdomyolysis.

Useful For: Assessing muscle damage from any cause

Interpretation: Elevated myoglobin levels are seen in conditions of acute muscle injury.

Reference Values:
< or =90 mcg/L


FMMPP 75594

MyoMarker 3 Plus Profile

Clinical Information: The MyoMarker Panel 3 Plus can be used to assist in the diagnosis of dermatomyositis, polymyositis and the anti-synthetase syndrome. Furthermore, it allows characterization of various subsets of these disorders and offers prognostic information.

Reference Values:
Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab, Anti-SRP Ab, Anti-Mi-2-Ab, Anti-U3 RNP (Fibrillarin), Anti-U2 RNP Ab, Anti-Ku Ab:
Reference Range: Negative

Interpretation for:
Anti-Jo-1 Ab, Anti-TIF-1gamma Ab, Anti-MDA-5-Ab (CADM-140), Anti-NXP-2 (P140) Ab, Anti-SAE1 Ab IgG, Anti-PM/Scl-100 Ab, Anti-SS-A 52kD Ab IgG, Anti-U1-RNP Ab:
Reference Range: <20
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FMYO3 75595

MyoMarker 3 Profile

Clinical Information: The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by muscle weakness, resulting from chronic muscle inflammation of unknown cause. Patients with IIM have a variety of autoantibodies with various clinical utilities that fall into two main groups. One group of autoantibodies are found in patients with myositis and are known as Myositis Specific Autoantibodies (MSA). The MSAs are highly specific for patients with polymyositis (PM) dermatomyositis (DM), anti-synthetase syndrome and necrotizing myositis. The second group of autoantibodies are considered Myositis Associated Autoantibodies (MAA). These appear in myositis overlap syndrome and in other connective tissue diseases, which correlate with certain clinical and/or pathophysiological conditions.

Reference Values:
Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab, Anti-SRP Ab, Anti-Mi-2-Ab, Anti-U3 RNP (Fibrillarin), Anti-U2 RNP Ab, Anti-Ku Ab:
Reference Range: Negative

Interpretation for:
Anti-Jo-1 Ab, Anti-TIF-1gamma Ab, Anti-MDA-5-Ab (CADM-140), Anti-NXP-2 (P140) Ab, Anti-PM/Scl-100 Ab, Anti-SS-A 52kD Ab IgG, Anti-U1-RNP Ab:
Reference Range: <20
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

**DDITF**

**Myxoid/Round Cell Liposarcoma, 12q13 (DDIT3 or CHOP) Rearrangement, FISH, Tissue**

**Clinical Information:** Myxoid/round cell liposarcoma is the second most common subtype of liposarcoma, accounting for more than one-third of all liposarcomas and representing about 10% of all adult soft-tissue sarcomas. Myxoid/round cell liposarcoma is described as a malignant tumor composed of uniform round to oval shaped primitive nonlipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma with a characteristic branching vascular pattern. A unique chromosome translocation, t(12;16)(q13;p11), resulting in a fusion of the DDIT3 gene (also known as CHOP or GADD153) on chromosome 12 and the FUS gene (also referred to as TLS) on chromosome 16, is the key genetic aberration in myxoid/round cell liposarcoma. More than 90% of myxoid/round cell liposarcoma are cytogenetically characterized by this translocation. In rare cases, a variant t(12;22)(q13;q12) has been described in which DDIT3 (CHOP) fuses with EWS, a gene highly related to FUS.

**Useful For:** Aiding in the diagnosis of myxoid/round cell liposarcoma by detecting a neoplastic clone associated with gene rearrangement involving the DDIT3 (CHOP) gene region at 12q13

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the DDIT3 (CHOP) probe. A positive result is consistent with a subset of myxoid/round cell liposarcoma. A negative result suggests no rearrangement of the DDIT3 (CHOP) gene region at 12q13. However, this result does not exclude the diagnosis of myxoid/round cell liposarcoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**G6SW**

**N-Acetylgalactosamine-6-Sulfatase, Leukocytes**

**Clinical Information:** Mucopolysaccharidosis IVA, (MPS IVA; Morquio A syndrome) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent...
**N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme activity.** The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (referred to as mucopolysaccharides: MPS or glycosaminoglycans: GAG). Accumulation of MPS in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms of MPS IVA are widely variable and affect multiple body systems. Clinical features may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Treatment options are mostly limited to symptom management; however, more recently available enzyme replacement therapy has shown to be effective in improving some function and quality of life for individuals with MPS IVA. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. A diagnostic workup in an individual with MPS IVA typically demonstrates elevated levels of urinary MPS and increased keratan sulfate and chondroitin-6-sulfate detected via quantitative and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Morquio B is a distinct disorder caused by a deficiency of beta-galactosidase and has a significant number of overlapping clinical features with MPS IVA. Enzyme analysis is necessary to distinguish between the 2 types. Reduced or absent activity of N-acetylgalactosamine-6-sulfate sulfatase enzyme in leukocytes and/or fibroblasts can confirm a diagnosis of MPS IVA. Sequencing of the GALNS gene allows for detection of disease-causing variants in affected patients and identification of familial variants allows for testing of at-risk family members.

**Useful For:** Preferred test to rule-out mucopolysaccharidosis IVA (Morquio A syndrome) The test is not useful for establishing carrier status for Morquio A syndrome.

**Interpretation:** Very low enzyme activity levels are consistent with mucopolysaccharidosis IVA (Morquio A syndrome).

**Reference Values:**
> or =92 nmol/17 hour/mg protein

**Clinical References:**

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**NAT2**

**83389**

**N-Acetyltransferase 2 Gene (NAT2), Full Gene Sequence, Whole Blood**

**Clinical Information:** Arylamine N-acetyltransferase type 2 (NAT2) is a highly polymorphic phase 2 metabolic enzyme that conjugates hydrazine derivatives and aromatic amine drugs with acetyl-groups. NAT2 also is involved in the acetylation and activation of some procarcinogens.(1) Individuals acetylate drugs at different rates by NAT2, and are described as having slow, intermediate, or fast acetylator phenotypes. A gradient exists in which the prevalence of slow acetylator phenotypes increases with decreasing distance to the equator. Near the equator, up to 80% of individuals may be slow acetylators, while in some more northern countries, as few as 10% of the population may have the slow acetylator phenotype. A number of drugs are metabolized by NAT2 including procainamide, dapsone, nitrazepam, hydralazine, zonisamide, and isoniazid. Isoniazid is used to treat and prevent tuberculosis, and is still used as a primary treatment agent. Adverse reactions with isoniazid, which include nausea, drug-induced hepatitis, peripheral neuropathy, and sideroblastic anemia, are associated more often with a slow NAT2 acetylator phenotype. These individuals may require a lower dose to avoid adverse reactions. The NAT2 gene contains a single intronless exon of 870 base pairs and encodes 290 amino acids. NAT2 is highly polymorphic and contains 16 known single nucleotide polymorphisms (SNPs) and 1 single base pair deletion. These polymorphisms are combined into 36 known haplotype alleles. Each individual haplotype is predictive of either a fast or slow acetylator phenotype. Individuals with 2 fast haplotypes are predicted to be extensive (normal) metabolizers, while those with 1 fast and 1 slow haplotype are intermediate.
metabolizers, and those with 2 slow haplotypes are poor metabolizers. (2,3) Studies with patients who have different acetylator haplotypes have correlated the ratio of plasma N-acetylisoniazid/isoniazid drug concentrations with haplotypes, with slow and intermediate acetylators having lower ratios than fast acetylators. (4) NAT2 Allele Nucleotide Change Amino Acid Change Predicted Acetylator Phenotype

| *4 | None None Fast | *5A 341T->C | 481C->T I114T Slow |
| *5B 341T->C | 481C->T | 803A->G I114T K268R Slow |
| *SC 341T->C | 803A->G I114T K268R Slow |
| *SD 341T->C | 5114T | 803A->G I114T K268R Slow |
| *SE 341T->C | 590G->A I114T K268R Slow |
| *SF 341T->C | 481C->T | 759C->T 803A->G I114T K268R Slow |
| *5G 282C->T 341T->C | 803A->G I114T K268R Slow |
| *SH 341T->C | 481C->T | 803A->G I89Ddel I114T K268R S287 Frameshift Slow |
| *5I 341T->C | 411A->T | 481C->T 803A->G I114T L137F K268R Slow |
| *5J 282C->T | 341T->C | 590G->A I114T R197Q Slow |
| *5K 282C->T | 341T->C | 590G->A I114T R197Q Slow |
| *5L 282C->T | 341T->C | 590G->A I114T R197Q Slow |
| *7A 857G->A | G286E Slow |
| *7B 282C->T | 857G->A | G286E Slow |
| *10 499G->A E167K Undetermined |
| *11A 481C->T None Undetermined |
| *11B 481C->T None Undetermined |
| *12A 803A->G K268R Fast |
| *12B 282C->T | 803A->G | K268R Fast |
| *12C 481C->T | 803A->G | K268R Fast |
| *12D 364G->A | 803A->G | D122N K268R Undetermined |
| *13 282C->T None Fast |
| *14A 191G->A | R64Q Slow |
| *14B 191G->A | 282C->T | R64Q Slow |
| *14C 191G->A | 341T->C | R64Q Slow |
| *14D 191G->A | 282C->T | R64Q Slow |
| *15E 191G->A | R64Q Slow |
| *15F 191G->A | 341T->C | R64Q Slow |
| *16 434A->C | Q145P Undetermined |
| *18 845A->C | K282T Undetermined |
| *19 190C->T | R64W Undetermined |

Useful For: Identifying patients who may require isoniazid dosing adjustments

Interpretation: The wild-type (normal) genotype for NAT2 is *4. This is the most commonly occurring allele in some, but not all, ethnic groups. (5) Individuals are classified as being slow, intermediate, or fast acetylators depending on their diplotypes. Slow acetylators have 2 slow haplotypes, fast acetylators have 2 fast haplotypes, and intermediate acetylators have 1 of each. Slow acetylators receiving isoniazid therapy should be monitored for signs of toxicity. Dose reductions may be considered for both slow and intermediate acetylators. However, it should be verified that the reduced isoniazid dose produces serum levels within the therapeutic range.

Reference Values:
An interpretive report will be provided.

Clinical References:

N-Methylhistamine, 24 Hour, Urine

Clinical Information: N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, particularly mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most, but not all, adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP. (1,2) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Diagnosis of mastocytosis is made by bone marrow
biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3-Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

**Useful For:** Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions using 24-hour urine collection specimens Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

**Interpretation:** Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

**Reference Values:**

**N-METHYLHISTAMINE**

- 0-5 years: 120-510 mcg/g creatinine
- 6-16 years: 70-330 mcg/g creatinine
- >16 years: 30-200 mcg/g creatinine

**CREATININE**

- Males: 930-2955 mg/24 hours
- Females: 603-1783 mg/24 hours

Reference values have not been established for patients who are less than 18 years of age.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

**Clinical References:**
produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most, but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP. Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH. Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3-Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

**Useful For:** Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions as a part of a profile Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

**Interpretation:** Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

**Reference Values:**
Only orderable as part of a profile. For more information see:

NMH24 / N-Methylhistamine, 24 Hour, Urine

- 0-5 years: 120-510 mcg/g creatinine
- 6-16 years: 70-330 mcg/g creatinine
- >16 years: 30-200 mcg/g creatinine

**Clinical References:**
**Clinical Information:** N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP. (1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH. (1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3-Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

**Useful For:** Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions as a part of a random urine collection profile. Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis.

**Interpretation:** Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation. UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

**Reference Values:**

Only orderable as part of a profile. For more information see:

NMHR / N-Methylhistamine, Random, Urine

- 0-5 years: 120-510 mcg/g creatinine
- 6-16 years: 70-330 mcg/g creatinine
- >16 years: 30-200 mcg/g creatinine

**Clinical References:**

**N-Methylhistamine, Random, Urine**

**Clinical Information:** N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most, but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3-Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

**Useful For:** Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions using random urine specimens Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

**Interpretation:** Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

**Reference Values:**
- 0-5 years: 120-510 mcg/g creatinine
- 6-16 years: 70-330 mcg/g creatinine
- >16 years: 30-200 mcg/g creatinine

**Clinical References:**
N-terminal Telopeptide, Serum

**Clinical Information:** Human bone is continuously remodeled through the process of bone formation and resorption. Measurement of bone turnover markers (BTM) in serum or urine serves as an indicator of bone formation or bone resorption cellular activities. BTM are physiologically elevated during childhood, growth, and during fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and of no diagnostic value. Bone diseases occur when formation and resorption are uncoupled. In these situations, BTM might serve as predictors of therapy response. Telopeptides of type 1 collagen are the most extensively studied and used bone resorption markers. There are 2 forms depending on the cross-link forming site with collagen: the N-terminal telopeptide (NTx) and C-terminal telopeptide (CTx), which are released during collagen degradation. In osteoporosis, a disease characterized by low bone mass and deterioration of bone tissue leading to increased skeletal fragility, measurement of BTM helps to determine treatment efficacy or patient's compliance with therapy. The advantage of measurement of BTM is that changes in response to therapy are observed within 3 to 6 months after therapy initiation; whereas changes in bone mineral density are not observed until 12 to 24 months posttherapy. Other diseases affecting the bone remodeling process, such as hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, bony metastases, as well as various congenital diseases of bone formation and remodeling, can result in accelerated and unbalanced bone turnover and elevation of BTM.

**Useful For:** Monitoring effectiveness of antiresorptive therapy in patients treated for osteoporosis or other metabolic bone disorders. As an adjunct in the diagnosis of medical conditions associated with increased bone turnover. This test is not useful for screening or diagnosing osteoporosis.

**Interpretation:** Elevated levels of N-terminal telopeptide (NTx) indicate increased bone resorption. A 30% or greater reduction in this resorption marker 3 to 6 months after initiation of therapy indicates a probably adequate therapeutic response. A common target of antiresorptive therapy in the treatment of postmenopausal osteoporosis is to achieve bone markers concentrations within the premenopausal reference range.

**Reference Values:**

All units are reported in nmol bone collagen equivalents (BCE)

- Adult (> or =18 years of age)
  - Males: 5.4-24.2 nmol BCE
  - Females: Premenopausal: 6.2-19.0 nmol BCE

The target value for postmenopausal adult females undergoing treatment for osteoporosis is the same as the premenopausal reference interval.

**Clinical References:**

NAbFeron (IFNB-1) Neutralizing Antibody Test

**Useful For:** Detection of antibodies to interferon-B-1

**Reference Values:**

Final report has been sent to the referring laboratory.
Clinical References: 

FNAD
80761

Nadolol, Serum/Plasma
Reference Values:
Reporting limit determined each analysis

Synonym(s): Corgard

Mean steady-state plasma levels following a daily regimen:
80 mg: 26 Â±â€œ 36 ng/mL
160 mg: 52 Â±â€œ 74 ng/mL
320 mg: 154 Â±â€œ 191 ng/mL

FNALO
91784

Naloxone - Total (Conjugated/Unconjugated), Screen, Urine
Reference Values:
Reporting limit determined each analysis (screen and confirmation)

Naloxone Â±â€œ Total ng/mL
Synonym(s): Narcan

Naloxone Â±â€œ Confirmation ng/mL
Synonym(s): Narcan

NAPSN
70519

Napsin A Immunostain, Technical Component Only
Clinical Information: Napsin A is an aspartic proteinase involved in the proteolytic processing of surfactant precursors in the normal alveolar epithelium. In normal tissues, napsin A is expressed in the cytoplasm of alveolar macrophages, type II pneumocytes, pancreatic ducts and acini, and in renal tubules. Napsin A has clinical utility for the identification of primary lung adenocarcinomas. Napsin A is also positive in a subset of thyroid and renal cell carcinomas (especially papillary types).

Useful For: Aids in the identification of primary lung adenocarcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Narcolepsy-Associated Antigen, HLA-DQB1 Typing, Blood

Clinical Information: Narcolepsy is a neurological condition affecting about 0.02% of African American, Caucasian, and Japanese individuals. It is characterized by excessive daytime somnolence and abnormal rapid eye movement (REM) sleep. Cataplexy (weakness precipitated by emotions, especially laughter) is present in 64% to 79% of patients with narcolepsy. Studies have identified DQB1*06:02 as a useful marker of narcolepsy. DQB1*06:02 is found in 90% to 95% of African American, Caucasian, and Japanese patients with narcolepsy who also have cataplexy (narcolepsy type 1), but only in 45% to 50% of patients with narcolepsy without cataplexy (narcolepsy type 2). It must also be clearly understood that about 25% of normal people have this gene. Because DQB1*06:02 is present in the normal population, no test for an HLA gene constitutes a test for narcolepsy. A more reliable approach would be to consider that, in an appropriate patient who has cataplexy, the absence of the strongly associated DQB1*06:02, provides good evidence that the patient does not have narcolepsy. However, its absence does not rule-out narcolepsy without cataplexy (narcolepsy type 2).

Useful For: Ruling out a diagnosis of narcolepsy

Interpretation: If DQB1*06:02 is not detected, the narcolepsy-associated antigen test result will be reported as negative for DQB1*06:02. If the allele is detected, the result will be reported as positive for DQB1*06:02.

Reference Values: An interpretive report will be provided.

antibody-dependent cellular cytotoxicity (ADCC) directed against antibody-coated target cells. (4) Circulating NK cells are enriched for the CD56(dim) phenotype, while within the lymph nodes, NK cells are largely CD56(bright). This differential localization is related to the pattern of homing receptors expressed on NK cells: CD56(dim) NK cells express homing markers for inflamed peripheral sites, while CD56(bright) NK cells express receptors for secondary lymphoid organs. The majority of circulating human NK cells, which have cytotoxic function and phenotype (CD56(dim)), are CD27-, while the CD56(bright) cells are CD27+. Therefore, the absence of CD27 expression identifies cytotoxic effector cells within the mature NK cell subsets. (5) Natural killer T (NKT) cells represent a specialized T-cell population that is distinct from conventional T cells. They express an invariant T-cell receptor (TCR) that recognizes self and bacterial glycosphingolipid antigens presented by the MHC class I-like molecule, CD1d. (11) The development of NKT cells is also unique from regular T cells, as NKT cell precursors are positively selected by CD4+CD8+ cortical thymocytes and the signaling pathways differ from the conventional T cells. Activated NKT cells rapidly produce large amounts of Th1 and Th2 cytokines that transactivate other immune components and, therefore, NK cells are involved in both innate and adaptive immune responses. (11) NK cell deficiencies can be present as part of a larger immunological syndrome or as an isolated deficiency. Some of the primary (monogenic) immunodeficiencies that affect NK cell function or numbers include autoimmune lymphoproliferative syndrome (ALPS) related to CASP8 (caspase 8 mutations); familial hemophagocytic lymphohistiocytosis (FHL) types 2, 3, and 4 due to mutations in the PFP1 (encoding perforin), UNC13D (encoding the Munc13-4 protein) and STX-11 (encoding syntaxin -11), respectively; Hermansky-Pudlak syndrome (AP3B1); Papillon-Lefèvre syndrome (CTSC, cathepsin C); nuclear factor kappa-beta essential modulator deficiency (NEMO) due to mutations in the IKBKGN gene; severe combined immunodeficiencies due to mutations in the IL-2RG, JAK3, ADA, PNP, ADK2 genes; bare lymphocyte syndrome (TAP2 gene); X-linked inhibitor of apoptosis deficiency (XIAP gene); X-linked lymphoproliferative disease (XLP): XLP-1 (due to mutations in the SAP gene); Griscelli syndrome (RAB27A gene); Chediak-Higashi syndrome (LYST gene); and Wiskott-Aldrich syndrome (WAS gene). (12) Patients with X-linked inhibitor of apoptosis protein (XIAP) deficiency have been variably reported as having either normal numbers of NK cells (13) or low numbers of NK cells. (14) The apparent discrepancy in the numbers of NK cells is likely related to the difference in size of the sample control groups and disease stage of patients between the 2 reports. At the present time, the role of NKT in development of NK cells has not been clearly delineated. The isolated NK cell deficiencies include the absolute NK cell deficiency (ANKD), the classic NK cell deficiency (CNKD), and the functional NK cell deficiency (FNKD). NK cell function is absent in ANKD and CNKD and deficient in FNKD, while NK cells are present in the latter but absent in the former 2 conditions. NKT cells are absent only in ANKD and present in both CNKD and FNKD. (12) NK cell dysfunction has also been reported in systemic juvenile rheumatoid arthritis and macrophage activation syndrome. (15) There is also more data emerging on the pathogenic role of NK cells in atopic and autoimmune diseases. (4) HIV-1 patients show a gradual loss of NK cells that correlates with disease progression. There is a selective loss of CD56(dim) NK cells, while the numbers of CD56(bright) NK cells remain the same. There appears to be a defect in differentiation from immature CD56- NK cells to mature CD56(dim) NK cells (16), with an expansion of the former (CD56-CD16+) NK cells in HIV viremic patients. (17) Differential mobilization of NK-cell subsets has also been reported related to acute exercise, with CD56(bright) NK cells being less responsive than CD56(dim) NK cells and the ratio of CD56(bright):CD56(dim) favors the former at least up to 1-hour post-exercise. (18) NK cells also play an important role in regulating viral infections, and their deficiency predisposes to susceptibility with herpes virus infections. NKG2D expression has been reported to decrease during human CMV infection. (19) NK cells that express inhibitory receptors to self-MHC class I molecules are called "licensed," which means they are functionally more responsive to stimulation, while "unlicensed" NK cells lack receptors for self-MHC class I and are hyporesponsive. Contrary to the hypothesis that "licensed" NK cells are key for viral immunity, the depletion of "unlicensed" NK cells impairs control of viremia, suggesting that these cells are critical for protection against viral infection. NK-cell lymphocytosis is seen in NK-neoplasias, extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia, and blastic NK-cell lymphoma. Chronic NK-cell lymphocytosis (CNKL) is an indolent disorder characterized by proliferation of CD3-CD56+CD16- NK cells. Epstein-Barr virus (EBV) can infect nonneoplastic NK cells (20), and there is an expansion of CD16+CD56(dim) NK cells. Chronic active EBV infection involving NK cells can present with severe inflammatory and necrotic skin reactions typically associated with EBV+ NK-cell lymphoproliferative disease. (21)

**Useful For:** Quantification of the major natural killer (NK)-cell subsets relative to total NK cells (NK cell subsets) or total lymphocytes (NK T cells) Assessment in the following clinical contexts: HIV,
primary immune deficiencies with NK cell defects, NK-cell lymphocytosis, solid-organ transplantation, immune reconstitution following bone marrow or hematopoietic cell transplantation, evaluation of NK cells in neoplasias This test is not useful for diagnosis or classification of NK cell malignancies. This test should not be used for assessing NK cell cytotoxic function.

**Interpretation:** Interpretive comments will be provided, where applicable, along with reference range values for adult samples. Since a separate pediatric reference range could not be established at this time, interpretation of pediatric samples will be made using the adult reference range as an approximate guideline.

**Reference Values:**
The appropriate age-related reference values will be provided on the report. Pediatric reference values are not available and therefore, interpretation will be based on adult ranges with appropriate cautionary statements in the interpretation.

**Clinical References:**

NERPC 113316

**Necropsy, regional (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**Necropsy, single organ (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

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**Necrotizing Myopathy Evaluation, Serum**

**Clinical Information:** Necrotizing autoimmune myopathy (NAM) is a serious, but rare muscle disease strongly associated with autoantibodies to either signal recognition protein (SRP) or 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). (1) NAM typically manifests with subacute proximal limb muscle weakness and persistently elevated serum creatine kinase (CK) concentrations, but slower onsets can occur and complicate diagnosis. Muscle biopsies in affected patients can demonstrate necrotic and regenerating myofibers without inflammatory infiltrates, suggesting the diagnosis. (2) However, sampling issues and lack of access to persons having expertise in obtaining, preparing, and interpreting muscle biopsy specimens may delay a diagnosis. (3) Early identification of NAM and subsequent aggressive immune-modulating therapy is critical. (1,3) Discovery of SRP- or HMGCR-IgG autoantibodies can aid in establishing an earlier diagnosis and treatment initiation. In addition, the discovery of SRP or HMGCR autoantibodies should prompt a search for an underlying malignancy. (4) Serial testing for these autoantibodies can delay diagnosis with the discovery of either antibody aiding in establishing an earlier diagnosis and treatment initiation. (1,3)

The clinical onsets are not specific to NAM consisting of proximal limb weakness in associations with an elevated serum creatinine kinase, with or without exposure to lipid lowering statin medications. (1,3-9) The clinical presentation can be confused with forms of inflammatory (dermatomyositis, polymyositis), toxic, metabolic or even neurodegeneration (ie, muscular dystrophy) and the diagnosis delayed without serological testing by SRP- or HMGCR-autoantibody testing. Panel testing of both HMGCR and SRP autoantibodies is the preferred strategy for the best patient care.

**Useful For:** Evaluating patients with suspected necrotizing autoimmune myopathy

**Interpretation:** Seropositivity for 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or signal recognition protein (SRP) autoantibodies supports the clinical diagnosis of necrotizing autoimmune myopathy (NAM). A paraneoplastic basis should be considered, according to age, sex, and other risk factors. In cases of NAM, immune therapy is required and often multiple simultaneously utilized immunotherapies are needed to successfully treat patients.

**Reference Values:**

- **3-Hydroxy-3-Methylglutaryl Coenzyme-A (HMG-CoA) Reductase:** <20.0 CU
- **Signal Recognition Particle Antibody Screen:** Negative
- **Signal Recognition Particle Antibody:** Negative
- **Signal Recognition Particle Antibody, Titer:** <1:240

**Clinical References:**
2. Emslie-Smith AM, Engel AG: Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular infiltration. Neurology 1991;41(6):936-939

**FNECT**

**Nectarine (Prunus spp) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**FNEFA**

**Nefazodone (Serzone)**

**Reference Values:**

Expected Nefazodone concentrations on recommended daily dosage regimens: 100 - 4000 ng/mL

**NEGCT**

**Negative Control, Technical Component Only**

**Clinical Information:** Patterns of protein expression as determined by immunohistochemistry can be useful for pathologic diagnosis and classification.

**Useful For:** Qualitative detection of protein expression within cells in paraffin-embedded tissues

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**MGRNA**

**Neisseria gonorrhoeae, Miscellaneous Sites, Nucleic Acid Amplification, Varies**

**Clinical Information:** Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common sexually transmitted infection (STI) with 301,174 cases of gonorrhea reported to CDC in 2009.(1,2) Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with
symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence).(1,2) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance.(2) Culture was previously considered to be the gold standard test for diagnosis of N. gonorrhoeae infection. However, organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(2-5) Immunoassays and non-amplification DNA tests are also available for N. gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT.(2-5) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.(2-5) Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Neisseria gonorrhoeae for non-FDA approved specimen types This test is not intended for use in medico-legal applications.

**Interpretation:** A positive result indicates the presence of rRNA of Neisseria gonorrhoeae. A negative result indicates that rRNA for N. gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N. gonorrhoeae), if appropriate.

**Reference Values:**
Negative

**Clinical References:**

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**GCRNA 61552**

**Neisseria gonorrhoeae, Nucleic Acid Amplification, Varies**

**Clinical Information:** Gonorrhea is caused by the bacterium Neisseria gonorrhoeae and is a common sexually transmitted infection (STI).(1,2) Many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, and/or rectal discharge. Potential complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups, such as those in communities with high STI...
prevalence).(1,2) Routine bacterial culture was previously considered the gold standard test for diagnosis of N gonorrhoeae infection. However, the bacteria are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(2-5) Immunoassays and non-amplification DNA tests are also available for N gonorrhoeae detection, but these methods are significantly less sensitive and specific than NAAT.(2-5) Improved screening and performance of NAAT testing has resulted in an increased number of accurately diagnosed cases.(2-5) Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of complications in women.

**Useful For:** Detection of Neisseria gonorrhoeae This test is not intended for use in medico-legal applications.

**Interpretation:** A positive result indicates the presence of rRNA of Neisseria gonorrhoeae. A negative result indicates that rRNA for N gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N gonorrhoeae), if appropriate.

**Reference Values:**
Negative


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**FNMEN 91669**

**Neisseria Meningitidis IgG Vaccine Response**

**Reference Values:**
Reference Ranges (pre-vaccination):

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>&lt; Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serogroup A</td>
<td>&lt;4.0 ug/mL</td>
</tr>
<tr>
<td>Serogroup C</td>
<td>&lt;5.0 ug/mL</td>
</tr>
<tr>
<td>Serogroup Y</td>
<td>&lt;4.0 ug/mL</td>
</tr>
<tr>
<td>Serogroup W-135</td>
<td>&lt;3.0 ug/mL</td>
</tr>
</tbody>
</table>

This assay measures serum IgG antibodies recognizing polysaccharide antigens from the four Neisseria meningitidis serogroups included in the licensed meningococcal vaccine. The meningococcal vaccine response is best evaluated by testing pre-vaccination and post-vaccination samples in parallel. A two-fold or greater increase for at least two sero-groups is expected when comparing post-vaccination to
pre-vaccination results. N. meningitidis IgG levels peak approximately one month post-vaccination, but decline markedly by two years.

**Neonatal Bilirubin, Serum**

**Clinical Information:** Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect one or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

**Interpretation:** The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is <20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

**Reference Values:**

**DIRECT**

> or =12 months: 0.0-0.3 mg/dL  
Reference values have not been established for patients who are <12 months of age.

**TOTAL**

0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.  7-14 days: <15.0 mg/dL  
15 days to 17 years: < or =1.0 mg/dL  
> or =18 years: < or =1.2 mg/dL

**Clinical References:**

Neopterin

**Clinical Information:** Neopterin, a pyrazolopyridine compound, is produced by macrophages after induction by interferon ? and serves as a marker of cellular immune system activation. Measurable levels of neopterin have been detected in both the serum and urine of patients suffering from various types of malignancies and viral infections. Changes in neopterin concentrations in serum or urine can predict complications such as graft rejection in organ transplant recipients. Elevated neopterin levels are found in autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Neopterin levels can be used as prognostic predictors for certain types of malignancies. Measurement of neopterin levels has particular value for monitoring patients infected with HIV. Neopterin is eliminated primarily in the urine, so evaluation of urinary neopterin levels may be useful in assessing activation of the cellular immunity system even in the absence of typical clinical symptoms, since a correlation has been observed with the course of diseases involving cellular immunity activation and urinary neopterin levels.

**Useful For:** Increased levels of neopterin are found during impaired renal function and viral infection in transplant patients. Elevated levels are also indicators for conditions related to impaired cellular immunity.

**Reference Values:**
Adults: <2.5 ng/mL

**Clinical References:**

Nettle, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to nettle Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
**Class IgE kU/L  Interpretation**

0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


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**NEUN**

**Neu-N Immunostain, Technical Component Only**

**Clinical Information:** Neuronal-nuclei (Neu-N) protein is expressed in neurons in the brain and ganglia in the peripheral nervous system. Presence of Neu-N has been correlated with the withdrawal of the neuron from the cell cycle and with terminal differentiation of the neuron

**Useful For:** Identification of neuronal nuclei

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**NELL1**

**Neural Epidermal Growth Factor-Like 1 Protein Immunostain, Technical Component Only**

**Clinical Information:** Primary membranous nephropathy is an autoimmune disease of the kidney where antibodies target an antigen in the glomerular basement membrane resulting in kidney damage or failure. In up to 75% of primary membranous nephropathy cases PLA2R and THSD7A are the target antigens. Recently neural epidermal growth factor-like 1 protein (NELL1) was identified as another target antigen for this pathology.

**Useful For:** Identification of neural epidermal growth factor-like 1 protein (NELL1) primary membranous nephropathy
**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**Neuro-Oncology Expanded Gene Panel with Rearrangement, Tumor**

**Clinical Information:** Molecular analysis of biomarkers is increasingly being used in oncology practice to support and guide diagnosis, prognosis, and therapeutic management. Molecular profiling has been incorporated in the World Health Organization classification of central nervous system (CNS) tumors and allows for robust delineation of diagnostic groups characterized by distinct molecular profiles with superior prognostic significance than histopathological classification alone. This test interrogates targeted regions across 187 genes associated with a variety of adult and pediatric CNS tumors to assess for the presence of somatic mutations and rearrangements, including mutations in IDH1/2, TERT, ATRX, TP53, H3F3A, HIST1H3B/C, BRAF, SMARCB1, and SMARCA4, and rearrangements involving RELA, BRAF, and EGFR (eg, EGFR vIII). See Targeted Gene Regions Interrogated by Neuro-Oncology Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying mutations and rearrangements that may support a diagnosis for patients with tumors of the central nervous system (CNS) Identifying mutations and rearrangements that may help determine prognosis for patients with tumors of the CNS Identifying specific mutations and rearrangements within genes known to be associated with response or resistance to specific cancer therapies

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**NF2F**

**Neurofilament (2F11) Immunostain, Technical Component Only**

**Clinical Information:** Neurofilament (NF) constitutes the main structural elements of neuronal axons and dendrites. NF subunits are present in neurons, neuronal processes, peripheral nerves, and sympathetic ganglion cells. In brain tissue, immunoperoxidase staining for NF labels the cytoplasm in the body of neurons and labels neuronal processes. Within tumors, only neoplastic cells of neural origin or those exhibiting neuronal differentiation have been observed to express NF. Positive immunostaining has been observed in neuromas, gangliogliomas, neuroblastomas, and medulloblastomas. Other tumors that can stain for NF include pheochromocytoma, chemodectomas, and carcinoid tumors.

**Useful For:** Aiding in the identification of neoplastic cells of neural origin or those exhibiting neuronal differentiation

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**NFSMI**

**Neurofilament (SMI31) Immunostain, Technical Component Only**

**Clinical Information:** Neurofilament antibody clone SMI 31 reacts with a phosphorylated epitope on neurofilament H and, to a lesser degree, neurofilament M. Both of these proteins contain multiple tandemly repeated serine phosphorylation sites. Clone SMI 31 reacts with thick and thin axons and specific dendrites such as basket cell dendrites. SMI 31 may also stain neuronal cell bodies in pathological conditions.

**Useful For:** Differentiating neurons (NF+) from glia (NF-)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester.

**Clinical References:**

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Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**PNEFS Neuroimmunology Antibody Follow-up, Serum**

**Clinical Information:** Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. The most commonly recognized cancers in this context are small-cell lung carcinoma (SCLC), thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Four classes of autoantibodies are recognized in serum analysis: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmatic (Purkinje cell cytoplasmatic antibody, type 1 [PCA-1], PCA-2, PCA-Tr, collapsin response-mediator protein-5 [CRMP-5], amphiphysin, and striational) -Gliarial nuclear (antiglial nuclear antibody) -Plasma membrane cation channel antibodies (neuronal P/Q-type and muscle acetylcholine receptor autoantibodies). These autoantibodies are potential effectors of neurological dysfunction. Patients who are seropositive usually present with subacute neurological symptoms and signs. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomnic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome (LES), myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

**Useful For:** Monitoring patients who have previously tested positive for one or more antibodies within the past 5 years in a Mayo Neuroimmunology Laboratory serum evaluation

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

**Reference Values:**

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<th>Test ID</th>
<th>Reporting Name</th>
<th>Methodology</th>
<th>Reference Value</th>
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<th>Test Description</th>
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<td>Cell Binding Assay (CBA)</td>
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<td>CBA</td>
<td>Negative</td>
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<td>Indirect Immunofluorescence Assay (IFA)</td>
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<td>AMPHS</td>
<td>Amphiphysin Ab, S</td>
<td>IFA</td>
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IGM_D IgM Disialo, GD1b EIA Negative
IMMTS IgM Monos GM1 Titer, S EIA
IGM_M IgM Monos, GM1 EIA Negative
ITPCS ITPR1 CBA, S CBA Negative
ITPTS ITPR1 IFA Titer, S IFA
ITPIIS ITPR1 IFA, S IFA
LGICS LGI1-IgG CBA, S CBA Negative
GLICS mGluR1 Ab CBA, S CBA Negative
GLITS mGluR1 Ab IFA Titer, S IFA
GLIIS mGluR1 Ab IFA, S IFA
VGKC Neuronal (V-G) K+ Channel Ab, S RIA < or =0.02 nmol/L
NFHCS NIF Heavy Chain CBA, S CBA Negative
NIFTS NIF IFA Titer, S IFA
NIFIS NIF IFA, S IFA
NFLCS NIF Light Chain CBA, S CBA Negative
NMDCS NMDA-R Ab CBA, S CBA Negative
NMDIS NMDA-R Ab IF Titer Assay, S IFA
CCN N-Type Calcium Channel Ab RIA < or =0.03 nmol/L
CCPQ P/Q-Type Calcium Channel Ab RIA < or =0.02 nmol/L
PC1BS PCA-1 Immunoblot, S IB Negative
PCTBS PCA-Tr Immunoblot, S IB
PCABP Purkinje Cell Cytoplasmic Ab Type 1 IFA
PCAB2 Purkinje Cell Cytoplasmic Ab Type 2 IFA
PCATR Purkinje Cell Cytoplasmic Ab Type Tr IFA
SRPIS SRP IFA Screen, S IFA
SRPTS SRP IFA Titer, S IFA
SRPBS SRP Immunoblot, S IB Negative


Neuroimmunology Antibody Follow-up, Spinal Fluid

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient’s humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response, and serve as serological markers of paraneoplastic autoimmunity. The most commonly recognized cancers in this context are small-cell lung carcinoma (SCLC), thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient’s autoantibody profile can predict a specific neoplasm with 90%
certainty, but not the neurological syndrome. Three classes of autoantibodies are recognized in the spinal fluid analysis: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmic (Purkinje cell cytoplasmic antibody, type 1 [PCA-1]; PCA-2; PCA-Tr, CRMP-5, and amphiphysin) -Glia nuclear (antiglial nuclear antibody: AGNA) Seropositive patients usually present with subacute neurological symptoms and signs. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome (LES), myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

**Useful For:** Monitoring patients who have previously tested positive for 1 or more antibodies within the past 5 years in a Mayo Clinic Neuroimmunology Laboratory spinal fluid evaluation

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient’s immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibodies to be detected, each predictive of the same cancer.

**Reference Values:**

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<tbody>
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<td>WBNC</td>
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<td>PCA1C</td>
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NMPAN 65434

Neuromuscular Genetic Panels by Next-Generation Sequencing (NGS), Varies

Clinical Information: Inherited neuromuscular disorders are a diverse group of diseases with heterogeneous genetic causes that affect the peripheral nervous system. The age of onset for these disorders ranges from in utero to old age. Based on the pattern of inheritance; clinical presentation; nerve conductions including, electromyography (EMG) pattern, and muscle and nerve biopsy findings; inherited neuromuscular disorders can be divided into major categories. These categories include muscular dystrophies, congenital muscular dystrophies, congenital myopathies, distal myopathies, ion channel hyperexcitable muscle diseases, metabolic myopathies, congenital myasthenic syndromes, hereditary motor and sensory neuropathies, hereditary motor neuropathies, motor neuron disorders, hereditary spastic paraplegias, and hereditary sensory neuropathies. Due to the considerable overlap in the clinical phenotypes of various neuromuscular disorders, it is often difficult to distinguish these specific inherited disorders from acquired forms without genetic testing. Additionally, even though most myopathies present with proximal shoulder and girdle weaknesses, some forms may present with distal weakness and, thereby, mimic neuropathies. Therefore, genetic testing can be extremely helpful in making the diagnosis. This is especially true for some genetic forms where neurophysiology may be ambiguous, as both neuropathy and myopathy exist simultaneously. Motor Neuron Disease (MND): MND selectively affect the motor neurons with degeneration. MND include 1) primary lateral sclerosis (PLS), 2) primary muscular atrophy (PMA), and 3) amyotrophic lateral sclerosis (ALS). In PLS and PMA, the motor neuron degeneration is limited to the upper motor neuron and lower motor neuron, respectively. The clinical phenotype of PLS can include gradual progressive leg weakness and spasticity and spastic bulbar weakness. In ALS, the most frequent form of MND, degeneration involves both upper and lower motor neurons and results in progressive muscle weakness, paralysis, and death from respiratory failure, usually within 3 to 5 years of disease onset. Muscular Dystrophy: Muscular dystrophies are characterized by skeletal muscle wasting. The muscular dystrophies can be subdivided into the dystrophinopathies, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophies, distal myopathies, and congenital muscular dystrophies. A clinical diagnosis is typically based on distribution and severity of muscular involvement, mode of inheritance, and other associated symptoms. The dystrophinopathies include Duchenne muscular dystrophy and Becker muscular dystrophy. These 2 forms are inherited in an X-linked manner and typically present with variable degrees of a limb-girdle pattern of weakness and can develop dilated cardiomyopathy. Limb-girdle muscular dystrophy is characterized by weakness and wasting predominately of the hips, shoulders, and proximal extremity muscles. Congenital muscular dystrophies are progressive early-onset muscle disorders that often have brain and other organ involvement. They are characterized by hypotonia, delayed motor development, and progressive weakness. Emery-Dreifuss Muscular Dystrophy: Emery-Dreifuss muscular dystrophy is characterized by the triad of joint contractures, slowly progressive muscle weakness and wasting, and cardiac involvement. Joint contractures usually being in early childhood and predominate in the elbows, ankles, and postcervical muscles. Age of onset, progression, and severity of disease demonstrate inter- and inframilial variability. Distal Myopathy: Distal myopathies are characterized by distal weakness and atrophy that starts in the muscles of the hands or feet and lack of cranial involvement or sensory loss. Distal myopathies are classified based on clinical features, inheritance pattern, and histopathological findings, such as the presence of rimmed vacuoles. Categories of distal myopathies include late adult-onset autosomal dominant forms, adult-onset autosomal dominant forms, early-onset autosomal dominant forms, early-onset autosomal recessive forms, and early adult-onset autosomal recessive forms. Additionally, inclusion body myositis presents with distal muscle weakness and may be in the differential with the distal myopathies. Myofibrillar Myopathy: Myofibrillar myopathies are characterized by slowly progressive weakness involving the proximal and distal muscles. The clinical phenotype can include...
peripheral neuropathy, cardiomyopathy, muscle stiffness, aching and cramps. While myofibrillar myopathies are typically adult onset disorders, individuals can present anywhere from early childhood through adulthood. Congenital Myopathy: Congenital myopathies are characterized by early-onset and specific histopathologic abnormalities on muscle biopsy. The clinical phenotype can include congenital hypotonia, generalized muscle weakness, delayed motor milestones, feeding difficulties, and facial muscle involvement. While congenital myopathies typically occur in childhood, individuals do occasionally present in adulthood. Also, individuals typically have slow progressive weakness, but in some cases the course may be severe. Congenital Myasthenic Syndrome: Congenital myasthenic syndromes are characterized by fatigable weakness involving ocular, bulbar, and limb muscles. The severity and disease course is highly variable, but individuals usually present in infancy or early childhood. The clinical phenotype associated with a neonatal onset can include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and muscle weakness. The clinical phenotype associated with a later childhood onset can include abnormal muscle fatigue, delayed motor milestones, ptosis, and extraocular muscle weakness. Metabolic Myopathy: Metabolic myopathies are a diverse group of inherited biochemical diseases involving limitation of the use of fuels by skeletal muscle to generate energy. These diseases can be categorized as disorders of lipid metabolism, glycogen and glucose metabolism, or mitochondrial myopathies that impair both lipid and glucose metabolism. Biochemical testing in multiple tissue types including blood, urine, and muscle, can help to determine which category of muscle disease is most likely. Disorders of fatty acid oxidation (FAO) are one category of metabolic myopathies characterized by hypoketotic hypoglycemia, hepatic dysfunction, skeletal myopathy, dilated and hypertrophic cardiomyopathy, and sudden or unexpected death. Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation during periods of fasting. Biochemical testing such as urine organic acids, plasma acylcarnitines, and fatty acids can aid in diagnosis. These test results are influenced by dietary factors and the clinical status of the patient, however, which often leads to incomplete diagnostic information or even false-negative results. Disorders of glycogen and glucose metabolism are another category of metabolic myopathies primarily affecting muscle and resulting in exercise intolerance, recurrent rhabdomyolysis, and myoglobinuria. Creatine kinase level is typically elevated during a major event. Muscle biopsy is often performed to verify absence of enzyme activity for the specific type of glycogenosis disease. Polyglucosan body disease involves progressive neurogenic bladder, spasticity and weakness causing gait difficulties from either primary muscle or nerve involvements, sensory loss mainly in the distal lower extremities, and mild cognitive difficulties such as executive dysfunction. Mitochondrial myopathy due to coenzyme Q10 (CoQ10) deficiency is a group of heterogenous diseases. These mitochondrial diseases are characterized by muscle weakness, exercise intolerance, elevated creatine kinase, and abnormal muscle biopsy findings. Skeletal Muscle Channelopathy: Nondystrophic myotonias are characterized by muscle stiffness generated by voluntary movement. Other features included transient or prolonged weakness, pain associated with myotonia, and fatigue. The nondystrophic myotonias include myotonia congenita, paramyotonia congenital, and sodium channel myotonia. The periodic paralyses are characterized by episodic attacks of weakness often triggered by diet or rest after exercise. They include hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and Andersen-Tawil syndrome. Rhabdomyolysis: Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers, which lead to leakage of potentially toxic cellular contents into the blood stream. The clinical severity can range from asymptomatic creatine kinase elevation to a life-threatening disease. The clinical features include acute-onset myalgia, transient muscle weakness, and pigmenteduria. Genetic causes of rhabdomyolysis include metabolic muscle disorders, mitochondrial disorders, disorders of intramuscular calcium release and excitation-coupling, and muscular dystrophies. Custom Gene Panel: Custom gene ordering allows the creation of a custom gene list to tailor testing to a patient’s exact need. After selection of a specific disease state, the custom gene panel can be modified to add or remove genes. Through this option single gene testing can be performed.

**Useful For:** Establishing a diagnosis of a neuromuscular disorder associated with known causal genes Serving as a second-tier test for patients in whom previous targeted gene mutation analyses for specific inherited neuromuscular disorder-related genes were negative Identifying mutations within genes known to be associated with inherited neuromuscular disorders, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or
possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Fluorescence-Activated Cell Sorting (FACS) Assay, Serum**

**Clinical Information:** Neuromyelitis optica (NMO), sometimes called Devic disease or optospinal multiple sclerosis [MS]) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders [NMOSD]) targeting the astrocytic water channel aquaporin-4 (AQP4).(1,2) Brain lesions are observed in >60% of patients with NMOSD and approximately 10% will be MS-like.(3) Children tend to have greater brain involvement than adults and brain lesions are more symptomatic than is typical for adult patients.(4) Extensive cerebral white matter signal abnormalities are sometimes encountered, most commonly in children, and are sometimes associated with encephalopathy. Circumventricular organs (CVO; eg, area postrema) are preferentially involved. Symptoms and signs attributable to area postrema involvement include intractable hiccups, nausea and vomiting, and these may occur in isolation, herald the onset of NMO or occur in association with the more classical optic neuritis or Longitudinally Extensive Transverse Myelitis (LETM).(5) Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Currently, in the AQP4-IgG era, 5 years after onset, approximately 30% of NMO patients will require a cane to walk and 10% will be wheelchair bound. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Skeletal muscle abnormalities with hyperCKemia have been reported in a few NMOSD patients. Recent reports indicate focal retinal vascular attenuation, inner nuclear layer thickening and microcystic edema in some NMO patients. The sensitivity and specificity of
Fluorescence-Activated Cell Sorting (FACS) assay for NMO is >80% and >99%, respectively. Detection of NMO/APQ4-IgG allows distinction of NMOSD from MS and is indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack, thereby reducing attack frequency and disability in the future.

**Useful For:**
- Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD)
- Diagnosis of autoimmune AQP4 channelopathy
- Diagnosis of neuromyelitis optica (NMO)
- Distinguishing NMOSD from multiple sclerosis early in the course of disease

**Interpretation:** A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months if NMOSD is suspected. This autoantibody is not found in healthy subjects.

**Reference Values:**
Negative

**Clinical References:**

---

**Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Fluorescence-Activated Cell Sorting (FACS) Assay, Spinal Fluid**

**Clinical Information:** Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD) targeting the astrocytic water channel aquaporin-4 (AQP4).(1,2) Brain lesions are observed in >60% of patients with NMOSD and approximately 10% will be MS-like.(3) Children tend to have greater brain involvement than adults and brain lesions are more symptomatic than is typical for adult patients.(4) Extensive cerebral white matter signal abnormalities are sometimes encountered, most commonly in children, and are sometimes associated with encephalopathy. Circumventricular organs (CVO; eg, area postrema) are preferentially involved. Symptoms and signs attributable to area postrema involvement include intractable hiccups, nausea and vomiting, and these may occur in isolation, herald the onset of NMO, or occur in association with the more classical optic neuritis or Longitudinally Extensive Transverse Myelitis (LETM).(5) Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Currently, in the AQP4-IgG era, 5 years after onset, approximately 30% of NMO patients will require a cane to walk and 10% will be wheelchair bound. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment...
promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Skeletal muscle abnormalities with hyperCKemia have been reported in a few NMOSD patients. Recent reports indicate focal retinal vascular attenuation, inner nuclear layer thickening and microcystic edema in some NMO patients. Detection of AQP4-IgG by NMO/AQP4 FACS in cerebrospinal fluid (CSF) allows distinction from MS and is indicative of an NMOSD. Though serum is optimal for AQP4-IgG testing, occasionally physicians submit only CSF for testing. A previous study, based on our first-generation indirect immunofluorescence assay compared the frequencies of AQP4-IgG in serum and CSF. The positivity rate was greater for serum alone than for CSF alone. However, testing of CSF was helpful when the serum was negative. Detection of AQP4-IgG in CSF allowed unambiguous distinction of NMO from MS. CSF testing offered the additional advantage of generally lacking the nonorgan-specific IgG autoantibodies (eg, antinuclear, antimitochondrial, and smooth muscle) that are common in serum of patients with NMO and also with classic paraneoplastic autoimmune disorders. Recent AQP4 FACS analysis of paired serum and CSF samples from 66 patients submitted for AQP4-IgG testing reveals a slightly better detection rate in serum (n=59) compared with CSF (n=55). All 7 patients who tested negative in serum also tested negative in CSF.

**Useful For:** Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Diagnosis of autoimmune AQP4 channelopathy Distinguishing NMOSD from multiple sclerosis early in the course of disease

**Interpretation:** A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. This autoantibody is not found in healthy subjects.

**Reference Values:**
Negative

**Clinical References:**

**Neuron-Specific Enolase (NSE), Spinal Fluid**

**Clinical Information:** Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron-specific enolase (NSE) is a 78 kDa gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF) are often elevated in diseases that result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum or CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jakob disease (CJD). NSE might also have utility as a prognostic marker in neuronal injury. For example, there is increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, in particular when caused by hypoxic insult.

**Useful For:** An auxiliary test in the diagnosis of Creutzfeldt-Jakob disease An auxiliary test in the
Interpretation: The diagnosis of Creutzfeldt-Jakob disease (CJD) is highly complex and involves clinical history and neurologic examination, detection of characteristic periodic sharp and slow wave complexes on electroencephalographs, magnetic resonance imaging (hyperintense basal ganglia), and exclusion of other possible causes of dementia, in addition to cerebrospinal fluid (CSF) examination. Consequently, patients are often diagnosed as having possible, probable, or definite CJD based upon the constellation of clinical findings. Detection of elevated CSF levels of NSE protein in these patients assists in the final diagnosis. A CSF neuron-specific enolase (NSE) within the normal reference range makes sporadic CJD very unlikely, but can be observed in less rapidly progressive forms of CJD, such as variant CJD related to infection with prions that cause bovine spongiform encephalopathy. With the previous Mayo Clinic-developed assay, in a group of carefully pre-selected patients with a probable diagnosis of CJD and an indeterminate or elevated NSE concentration in CSF, the respective diagnostic sensitivities of approximately 87% and approximately 80%, and diagnostic specificities of approximately 66% and approximately 83% were observed. Small cell lung carcinoma central nervous system metastases, particularly if they involve the leptomeninges, will lead to, usually substantial, elevations in CSF NSE concentrations.

Reference Values:
- Normal: < or =15 ng/mL
- Indeterminate: 15-30 ng/mL
- Elevated: >30 ng/mL

Elevated results may indicate the need for additional workup. Possible causes may be NSE-secreting central nervous system/leptomeningeal tumor or rapid neuronal destruction from a variety of causes. In the context of dementia, elevated results may be suggestive of Creutzfeldt-Jakob disease.

Clinical References:
controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### Neuron-Specific Enolase, Serum

**Clinical Information:**
Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron specific enolase (NSE) is a 78 kDa gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ-specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF), are often elevated in diseases that result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum or CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jacob Disease. NSE might also have utility as a prognostic marker in neuronal injury. For example, there is increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, particularly when caused by hypoxic insult. NSE is also frequently overexpressed by neural crest-derived tumors. Up to 70% of patients with small cell lung carcinoma (SCLC) have elevated serum NSE concentrations at diagnosis, and approximately 90% of patients with advanced SCLC will have serum levels above the healthy reference range. Other neuroendocrine tumors with frequent expression of NSE include carcinoids (up to 66% of cases), islet cell tumors (typically <40% of cases), and neuroblastoma (exact frequency of NSE expression unknown). NSE levels in NSE-secreting neoplasms correlate with tumor mass and tumor metabolic activity. High levels have therefore some negative prognostic value. Falling or rising levels are often correlated with tumor shrinkage or recurrence, respectively.

**Useful For:**
- A follow-up marker in patients with neuron-specific enolase-secreting tumors of any type
- An auxiliary test in the diagnosis of small cell lung carcinoma
- An auxiliary test in the diagnosis of carcinoids, islet cell tumors and neuroblastomas
- An auxiliary tool in the assessment of comatose patients

**Interpretation:**
Serum neuron-specific enolase (NSE) measurement has its greatest utility in the follow-up of patients with tumors of any type that have been shown to secrete NSE. With successful treatment, serum concentrations should fall with a half-life of approximately 24 hours. Persistent NSE elevations in the absence of other possible causes (see Cautions) suggest persistent tumor. Rising levels indicate tumor spread or, in patients who had previously become NSE negative, recurrence. In the context of a patient with a lung mass, disseminated malignancy of unknown origin or symptoms suggestive of paraneoplastic disease without identifiable tumor, elevated NSE suggests an underlying small cell lung carcinoma (SCLC). In patients with suspected carcinoid, islet cell tumor, or neuroblastoma, who have no clear elevations in the primary tumor markers used to diagnose these conditions, an elevated serum NSE level supports the clinical suspicion. -Carcinoid: chromogranin A, urinary 5-hydroxyindoleacetic acid, serum/blood 5-hydroxytryptamine -Islet cell tumors: variety of peptide and amine-derived hormones, chromogranin A -Neuroblastoma: vanillylmandelic acid and homovanillic acid When considered alongside established outcome predictors of coma, such as Glasgow coma scale and other clinical predictors (papillary light responses, corneal reflexes, motor responses to pain, myoclonus, status...
epilepticus), electroencephalogram, sensory evoked potentials, measurement of serum NSE concentrations provides additional information. Elevated levels are indicative of a poor outcome. Currently, no established algorithms exist to combine serum NSE concentrations and the various other predictors into a composite score that gives clear predictive outcome information. The NSE measurement therefore needs to be considered in a qualitative or semi-quantitative fashion and carefully weighed against other predictors by a physician experienced in examining and managing coma patients.

Reference Values:
* or =15 ng/mL

Serum markers are not specific for malignancy, and values may vary by method.

Clinical References:


NCLGP 608014

Neuronal Ceroid Lipofuscinosis (Batten Disease) Gene Panel, Varies

Clinical Information: Neuronal ceroid lipofuscinoses (NCL) are a subset of lysosomal storage diseases that involve defective cellular processing of lipids. NCL are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophilic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles (FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms. Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult onset form (ANCL; DNAJC5 gene) has been shown to be autosomal dominant.

Useful For: Follow up for abnormal biochemical or electron microscopy results suspicious for neuronal ceroid lipofuscinoses (NCL) Establishing a molecular diagnosis for patients with NCL Identifying variations within genes known to be associated with NCL, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

Neuronal Ceroid Lipofuscinosis (Batten Disease) Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Neurotensin

Clinical Information: Neurotensin is a 13 amino acid peptide produced primarily by endocrine cells of the ileal mucosa. Physiological actions of Neurotensin include hypertension, vasodilation, hyperglycemia, and inhibition of gastric motility. Its C-terminus is similar to Angiotensin I. It is a potent analgesic affecting hypothermia, muscle relaxation, and decreased motor activity. Pancreatic Polypeptide secretion is strongly stimulated by Neurotensin. Neurotensin appears to cause the release of Luteinizing Hormone-Releasing Hormone and Corticotropin Releasing Hormone effecting the release of Luteinizing Hormone, Follicle Stimulating Hormone, and ACTH but not Thyroid Stimulating Hormone or Growth Hormone. Neurotensin also stimulates pancreatic bicarbonate and intestinal secretion. Neurotensin levels are stimulated by food and Bombesin. Elevated levels have been found in pancreatic endocrine tumors, Oat Cell, Squamous, and Adeno Carcinomas. Elevated levels have been found to cause watery diarrhea.

Reference Values:
50 - 100 pg/mL

Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (CSF)

Clinical Information: CSF Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (NC04) is useful for diagnosis of certain disorders of neurotransmitter metabolism. This testing may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL Monoamine metabolite testing includes homovanillic acid (HVA), 3-O-methyl-Dopa (3-OMD), and 5-hydroxyindole acetic acid (5-HIAA). This test is useful in diagnosing pediatric neurotransmitter diseases affecting dopamine and serotonin metabolism in the brain. Inborn errors of metabolism and various drugs may lead to severe imbalances and disturbances in these neurotransmitter systems that are reflected by changes in the concentration of monoamines metabolites in CSF. Primary inherited defects involve deficiencies in tyrosine and tryptophan hydroxylase, aromatic amino acid decarboxylase, monoamine oxidase, dopamine beta hydroxylase and the dopamine transwporter. Other defects in the biopterin synthesis pathway may also affect dopamine and serotonin metabolism. These disorders are characterized by a wide range of symptoms that may include developmental delay, mental disability, behavioral disturbances, dystonia, seizures, encephalopathy, athetosis and ptosis.

Interpretation:

Reference Values:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>3-O-MD (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>208-1159</td>
<td>337-1299</td>
<td>&lt;300</td>
</tr>
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</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
FNTSM 91940

**Neurotransmitter Profile 3**

**Reference Values:**

5-Methyltetrahydrofolate

<table>
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<th>Age (years)</th>
<th>5MTHF (nmol/L)</th>
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<tbody>
<tr>
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<td>0.2-0.5</td>
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<td>0.5-2.0</td>
<td>40-187</td>
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<tr>
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<td>40-128</td>
</tr>
<tr>
<td>10-15</td>
<td>40-120</td>
</tr>
<tr>
<td>Adults</td>
<td>40-120</td>
</tr>
</tbody>
</table>

Neurotransmitter Metabolites/Amines

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>3-O-MD (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>208-1159</td>
<td>337-1299</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>179-711</td>
<td>450-1132</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>129-520</td>
<td>294-1115</td>
<td>&lt;300</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>74-345</td>
<td>233-928</td>
<td>&lt;150</td>
</tr>
<tr>
<td>5.0-10</td>
<td>66-338</td>
<td>218-852</td>
<td>&lt;100</td>
</tr>
<tr>
<td>10-15</td>
<td>67-189</td>
<td>167-563</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Adults</td>
<td>67-140</td>
<td>145-324</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Tetrahydrobiopterin/Neopterin Profile

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BH4 (nmol/L)</th>
<th>Neop (nmol/L)</th>
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</thead>
<tbody>
<tr>
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<td>7-40</td>
</tr>
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<td>10-15</td>
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<td>8-33</td>
</tr>
<tr>
<td>Adults</td>
<td>10-30</td>
<td>8-28</td>
</tr>
</tbody>
</table>

Interpretation performed by Keith Hyland, Ph.D.

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

DISCLAIMER required by the FDA for high complexity clinical laboratories: HPLC testing was developed and its performance...
Newborn Aneuploidy Detection, FISH

Clinical Information: Approximately half of clinically recognizable spontaneous abortions have a major chromosomal anomaly. Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8/1,000 have a major chromosome anomaly, of which 6.5/1,000 involve aneuploidy of 1 of these 5 chromosomes. Diagnosis of chromosomal disorders can be performed by chromosome analysis of uncultured blood, standard chromosome study, and the technique utilizing FISH based on interphase cells. Standard chromosome analysis takes 3 to 10 days and analysis from uncultured newborn blood is often unsatisfactory and labor-intensive. FISH based methods facilitate rapid diagnosis of aneuploidy and may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes. This test does not detect chromosomal aneuploidies other than 13, 18, 21, X, and Y or any structural anomaly that does not result in gain of these chromosomes. Low levels of mosaicism involving chromosomes 13, 18, 21, X, or Y may not be detected by this assay.

Useful For: Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in newborn peripheral blood specimens

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

Next-Generation Sequencing Acute Myeloid Leukemia,
Therapeutic Gene Mutation Panel (FLT3, IDH1, IDH2, TP53), Varies

Clinical Information: Next-generation sequencing (NGS) is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can provide critical prognostic information and may help in guiding therapeutic management decisions by physicians, particularly if targeted therapies are available.

Useful For: Evaluation of acute myeloid leukemia (AML) using a focused 4-gene panel at the time of diagnosis, or possibly relapsed or refractory disease, to help determine optimal (eg, targeted) therapeutic approaches

Interpretation: Mutations (gene alterations) identified, if present, using human reference genome build GRCh37 (hg19). An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:
Next-Generation Sequencing, Acute Myeloid Leukemia, 11-Gene Panel, Varies

Clinical Information: Next-generation sequencing (NGS) is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can provide critical prognostic information and may help in guiding therapeutic management decisions by physicians, particularly if targeted therapies are available.

Useful For: Evaluation of acute myeloid leukemia (AML) using a focused 11-gene panel at the time of diagnosis or possibly at relapsed/refractory disease, to assist in appropriate classification, prognosis, and therapeutic management of patients Evaluation to determine if a different gene mutation profile is present at the time of AML relapse

Interpretation: Mutations (gene alterations) identified, if present, using human reference genome build GRCh37 (hg19). An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


Next-Generation Sequencing, Reflex from Acute Myeloid Leukemia 4- or 11-Gene Panels, Varies

Clinical Information: Next-generation sequencing (NGS) is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many myeloid neoplasms lack a clonal cytogenetic finding at diagnosis (normal karyotype) but can be diagnosed and classified according to the gene mutation profile. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and sometimes therapeutic information for the managing physicians.

Useful For: When a more targeted gene panel test was initially performed in our laboratory, this test allows for comprehensive reanalysis of a larger set of genes/gene regions Evaluation of hematologic neoplasms, specifically of myeloid origin (eg, acute myeloid leukemia, myelodysplastic syndrome,
myeloproliferative neoplasm, myelodysplastic/myeloproliferative neoplasm) at the time of diagnosis or possibly disease relapse, to help determine diagnostic classification and provide prognostic or therapeutic information for clinical management.

**Interpretation:** Only orderable as a reflex within 6 months of initial testing. For more information see NGAMT / Next-Generation Sequencing Acute Myeloid Leukemia, Therapeutic Gene Mutation Panel (FLT3, IDH1, IDH2, TP53) or NGAML / Next-Generation Sequencing, Acute Myeloid Leukemia, 11-Gene Panel. Mutations (gene alterations) identified, if present, using reference genome build GRCh37 (hg19). An interpretive report will be provided. If this test is ordered in the setting of erythrocytosis and suspicion of polycythemia vera, interpretation requires correlation with a concurrent or recent prior bone marrow evaluation.

**Reference Values:**
Only orderable as a reflex. For more information see NGAMT / Next-Generation Sequencing Acute Myeloid Leukemia, Therapeutic Gene Mutation Panel (FLT3, IDH1, IDH2, TP53) or NGAML / Next-Generation Sequencing, Acute Myeloid Leukemia, 11-Gene Panel.

An interpretive report will be provided.

**Clinical References:**

**Nickel, 24 Hour, Urine**

**Clinical Information:** Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes but has no known role in humans. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as substances known as catalysts that increase the rate of chemical reactions. One of the most toxic nickel compounds is nickel carbonyl, Ni(CO)4, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4 is very toxic. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the major source of exposure to Ni. Foods naturally high in Ni concentrations include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing Ni. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in artificial body parts made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to Ni. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or nickel-processing plants. Urine is the specimen of choice for the determination of Ni exposure but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

**Useful For:** Preferred test for biomonitoring patients for nickel exposure to minimize any potential
**Diurnal Variation**

**Interpretation:** Values of 3.6 mcg/24-hour specimen and higher represent possible environmental or occupational exposure. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.

**Reference Values:**
- 0-17 years: not established
- ≥18 years: <3.6 mcg/24h

**Clinical References:**

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**Nickel, Serum**

**Clinical Information:** Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes but has no known role in humans. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as substances known as catalysts that increase the rate of chemical reactions. One of the most toxic Ni compounds is nickel carbonyl, Ni(CO)4, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4 is very toxic. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the major source of exposure to Ni. Foods naturally high in Ni include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to nickel by breathing air, drinking water, or smoking tobacco containing Ni. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in artificial body parts made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to Ni. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or nickel-processing plants. Urine is the specimen of choice for the determination of Ni exposure but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

**Useful For:** Confirmation of an elevated urinary nickel concentration This test is not useful for the investigation of nickel hypersensitivity.

**Interpretation:** Values 2.0 ng/mL and higher represent possible environmental or occupational exposure to nickel (Ni). Toxic Ni concentrations are greater or equal to 10 ng/mL. Normal Ni values are based on a Mayo Clinic study using healthy volunteers. Toxic values have been deduced from observation and unpublished internal study. Clinical concern about Ni toxicity should be limited to patients with potential for exposure to toxic Ni compounds. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.
**Reference Values:**

<2.0 ng/mL


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**Nickel/Creatinine Ratio, Random, Urine**

**Clinical Information:** Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes but has no known role in humans. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as substances known as catalysts that increase the rate of chemical reactions. One of the most toxic Ni compounds is nickel carbonyl, Ni(CO)₄, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)₄ is very toxic. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the major source of exposure to Ni. Foods naturally high in Ni include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing nickel. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in artificial body parts made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to it. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or Ni-processing plants. Urine is the specimen of choice for the determination of Ni exposure but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

**Useful For:** Preferred specimen type for biomonitoring nickel exposure

**Interpretation:** Values of 3.8 mcg/g creatinine and higher for male patients, or 4.3 mcg/g creatinine and higher for female patients, represent possible environmental or occupational exposure to nickel (Ni). Ni concentrations above 50 mcg/g creatinine are of concern, suggesting excessive exposure. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.

**Reference Values:**

- 0-17 years: not established
  - Males > or =18 years: <3.8 mcg/g creatinine
  - Females > or =18 years: <4.3 mcg/g creatinine


NICOU 82510

**Nicotine and Metabolites, Random, Urine**

**Clinical Information:** Tobacco use is the leading cause of death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe, cigar, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine is rapidly metabolized in the liver to cotinine, exhibiting an elimination half-life of 2 hours. Cotinine exhibits an apparent elimination half-life of 15 hours. Patients using tobacco products excrete nicotine in urine in the concentration range of 1,000 to 5,000 ng/mL. Cotinine accumulates in urine in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users excrete cotinine in the range of 1,000 to 8,000 ng/mL. Urine concentrations of nicotine and metabolites in these ranges indicate the subject is using tobacco or is receiving high-dose nicotine patch therapy. In addition to nicotine and metabolites, tobacco products also contain other alkaloids that can serve as unique markers of tobacco use. Two such markers are anabasine and nornicotine. Anabasine is present in tobacco products, but not nicotine replacement therapies. Nornicotine is present as an alkaloid in tobacco products and as a metabolite of nicotine. The presence of anabasine greater then 10 ng/mL or nornicotine greater then 30 ng/mL in urine indicates current tobacco use, irrespective of whether the subject is on nicotine replacement therapy. The presence of nornicotine without anabasine is consistent with use of nicotine replacement products. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit urine nicotine values below 30 ng/mL, cotinine values below 50 ng/mL, anabasine levels below 2 ng/mL, and nornicotine levels below 2 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Urine cotinine has been observed to accumulate up to 20 ng/mL from passive exposure. Neither anabasine nor nornicotine accumulates from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in a random urine specimen to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate. Quantification of urine nicotine and metabolites while a patient is actively using a tobacco product is useful to define the concentrations that a patient achieves through self-administration of tobacco. Nicotine replacement dose can then be tailored to achieve the same concentrations early in treatment to assure adequate nicotine replacement so the patient may avoid the strong craving they may experience early in the withdrawal phase. This can be confirmed by measurement of urine nicotine and metabolite concentrations at steady-state (2-3 days after replacement therapy is started). Once the patient is stabilized on the dose necessary to achieve complete replacement and responding well to therapy, the replacement dose can be slowly tapered to achieve complete withdrawal.

**Useful For:** Monitoring tobacco use Monitoring patients on nicotine-replacement therapy for concurrent use of tobacco products

**Interpretation:** Urine nicotine in the range of 1,000 to 5,000 ng/mL with cotinine in the range of 1,000 to 8,000 ng/mL indicates the subject is either actively using a tobacco product or on high-dose nicotine patch therapy. The presence of anabasine and nornicotine indicates a subject on patch therapy who is actively using a tobacco product. Typical findings are as follows: While using a tobacco product:
- Peak nicotine concentration: 1,000 to 5,000 ng/mL -Peak cotinine concentration: 1,000 to 8,000 ng/mL
- Anabasine concentration: 10 to 500 ng/mL -Nornicotine concentration: 30 to 900 ng/mL Tobacco user after 2 weeks complete abstinence:
- Nicotine concentration: <30 ng/mL -Cotinine concentration: <50 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL Nontobacco user with passive exposure:
- Nicotine concentration: <20 ng/mL -Cotinine concentration: <20 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL Nontobacco user with no passive exposure:
- Nicotine concentration: <5.0 ng/mL -Cotinine concentration: <5.0 ng/mL
- Anabasine concentration: <2.0 ng/mL
- Nornicotine concentration: <2.0 ng/mL

**Reference Values:**

Non-tobacco user with no passive exposure:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICOTINE</td>
<td>&lt;5.0 ng/mL</td>
</tr>
<tr>
<td>COTININE</td>
<td>&lt;5.0 ng/mL</td>
</tr>
<tr>
<td>ANABASINE</td>
<td>&lt;2.0 ng/mL</td>
</tr>
<tr>
<td>NORNICOTINE</td>
<td>&lt;2.0 ng/mL</td>
</tr>
</tbody>
</table>


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**Nicotine and Metabolites, Serum**

**Clinical Information:** Fatalities related to tobacco use are a leading cause of death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of approximately 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 24 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values <3.0 ng/mL and cotinine <3.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

**Useful For:** Monitoring tobacco use

**Interpretation:** Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using a tobacco product, see NICOU / Nicotine and Metabolites, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products, indicates recent tobacco use. Typical findings are as follows: While using a tobacco product: - Peak nicotine concentration: 30 to 50 ng/mL - Peak cotinine concentration: 200 to 800 ng/mL * Higher values may be seen in subjects with high cytochrome P450 2D6 activity Tobacco user after 2 weeks complete abstinence: - Nicotine concentration: <3.0 ng/mL - Cotinine concentration: <8.0 ng/mL Nontobacco user with passive exposure: - Nicotine concentration: <3.0 ng/mL - Cotinine concentration: <8.0 ng/mL Nontobacco user with no passive exposure: - Nicotine concentration: <3.0 ng/mL - Cotinine concentration: <3.0 ng/mL
Reference Values:
NICOTINE
<3.0 ng/mL

COTININE
<3.0 ng/mL


Nicotine Survey, Serum

Clinical Information: Fatalities related to tobacco use are a leading cause of death in United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of approximately 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 24 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values less than 3.0 ng/mL and cotinine less than 3.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

Useful For: Monitoring tobacco use

Interpretation: Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using tobacco products, see NICOU / Nicotine and Metabolites, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products, indicates recent tobacco use. Typical findings are as follows: While using a tobacco product: -Peak nicotine concentration: 30 to 50 ng/mL -Peak cotinine concentration: 200 to 800 ng/mL* *Higher values may be seen in subjects with high cytochrome P450 2D6 activity Tobacco user after 2 weeks complete abstinence: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <3.0 ng/mL Nontobacco user with passive exposure: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <8.0 ng/mL Nontobacco user with no passive exposure: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <3.0 ng/mL

Reference Values:
NICOTINE
<3.0 ng/mL

COTININE
<3.0 ng/mL

Niemann-Pick Disease, Types A and B, Full Gene Analysis, Varies

Clinical Information: Niemann-Pick disease (types A and B) is an autosomal recessive lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is generally milder, though variable in its clinical presentation. Most type B patients do not have neurologic involvement and survive to adulthood. Variants in the SMPD1 gene are responsible for the clinical manifestations of Niemann-Pick disease types A and B. Although this disease is panethnic, it has a significantly higher frequency in individuals of Ashkenazi Jewish and Northern African descent. The carrier rate for type A in the Ashkenazi Jewish population is 1 in 90 individuals. There are 3 common variants in the Ashkenazi Jewish population: L302P, R496L, and fsP330, which account for approximately 97% of variant alleles in this population. The deltaR608 alteration accounts for approximately 90% of the type B variant alleles in individuals from the Maghreb region of North Africa and 100% of the variant alleles in Gran Canaria Island. For diagnostic testing, analysis of the acid sphingomyelinase enzyme (ASMW / Acid Sphingomyelinase, Leukocytes) and OXNP / Oxysterols, Plasma should be performed prior to targeted mutation analysis or full gene analysis.

Useful For: Confirmation of a diagnosis of Niemann-Pick disease type A or B Carrier screening in cases where there is a family history of Niemann-Pick disease type A or B, but disease-causing variants have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Niemann-Pick Type C Detection, Fibroblasts

Clinical Information: Niemann-Pick disease type C (NPC) is an autosomal recessive lipid storage disorder resulting from variants in either the NPC1 (95% of cases) or NPC2 genes. Impaired cellular cholesterol trafficking results in progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. NPC has a variable age of onset (range: perinatal period to adulthood) and a highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated
with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. Measurement of oxysterols (products of cholesterol oxidation) are an effective, quick, and less invasive option for screening in an individual with suspected NPC (see OXNP / Oxysterols, Plasma; OXYBS / Oxysterols, Blood Spot; OXYWB / Oxysterols, Blood). Elevated levels of cholestane-3-beta, 5-alpha, 6-beta-triol (COT), lyso-sphingomyelin 509 (LSM 509), and 7-ketocholesterol (7-KC) may be seen; however, individuals with cholestasis may also present with this finding. Molecular testing of NPC1 and NPC2 (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis) is helpful for disease confirmation, but may reveal variants of unknown significance, heterozygosity, or absence of genetic variants in a patient with presumed NPC. Demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts can be used to assess the functional significance of NPC1 or NPC2 variants and is helpful for disease confirmation in cases with a high clinical suspicion of NPC with ambiguous oxysterol results or cases where molecular testing is not informative.

**Useful For:** Diagnosis of Niemann-Pick disease type C This test is not useful for Niemann-Pick disease type C carrier detection.

**Interpretation:** Values expected in Niemann-Pick disease type C are below 10% of that found in normal cultured fibroblasts. Values between 10% and 80% of normal will have to be judged on other diagnostic criteria. All values will be followed up by filipin staining for cholesterol.

**Reference Values:**
If the results indicate that the patient's cultured fibroblasts esterify cholesterol at a level that is <10% of normal cultured fibroblasts and when filipin staining shows excessive storage of free cholesterol, it will be stated that the patient is positive for Niemann-Pick type C disease. All samples will be stained by filipin to see if a milder biochemical phenotype is the likely cause of the Niemann-Pick disease-like clinical picture.


**NPCZ 35518**

**Nieman-Pick Type C Disease, Full Gene Analysis, Varies**

**Clinical Information:** Niemann-Pick type C (NPC) is an inherited disorder of cholesterol transport that results in an accumulation of unesterified cholesterol and lipids in the lysosomal/endosomal system and in various tissues. Although NPC belongs to a group of lysosomal disorders including Niemann-Pick types A and B, these diseases are metabolically and genetically distinct. Niemann-Pick types A and B are caused by variant in the SMPD1 gene, which encodes the enzyme sphingomyelinase, whereas NPC is caused by variants in the NPC1 or NPC2 genes. The incidence of NPC is approximately 1 in 120,000 to 1 in 150,000 live births. Age of onset is variable and ranges from the perinatal period to adulthood. Clinical presentation is also highly variable. Infants may present with or without liver disease (hepatosplenomegaly) and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Adult-onset
NPC is associated with a slower progression and is characterized by neurologic and psychiatric problems. NPC is inherited in an autosomal recessive manner, in which affected individuals carry 2 variants in either the NPC1 or NPC2 gene. Most variants are family specific, although there are 2 variants in the NPC1 gene that are more common than others. The G992W alteration is common in the French Acadian population of Nova Scotia. The I1061T alteration is the most common variant worldwide, and is seen in patients of Hispanic and Western European (United Kingdom and France) descent. Full gene sequencing and analysis for large deletions and duplications of the NPC1 and NPC2 genes detect less common disease-causing variants. The recommended first-tier test to screen for NPC is a biochemical test measuring oxysterols (OXNP / Oxysterols, Plasma). Molecular testing provides confirmation of a biochemical diagnosis or a basis for carrier testing of family members. Individuals with abnormal biochemical results are more likely to have 2 identifiable variants by molecular testing. Additionally, cholesterol esterification coupled with filipin staining on a fibroblast specimen (NIEM / Niemann-Pick Type C Detection, Fibroblasts) can aid in diagnosis.

**Useful For:** Second-tier test for confirming a biochemical diagnosis of Niemann-Pick type C (NPC) Carrier testing of individuals with a family history of NPC in cases when an affected individual is not available for testing or disease-causing variants have not been identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Nitrogen, Total, 24 Hour, Urine**

**Clinical Information:** Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine; however, fecal nitrogen can account for 30% to 50% of total nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of protein catabolism and, therefore, urine and fecal nitrogen may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

**Useful For:** Assessing nutritional status (protein malnutrition) Assessment of protein nutrition and nitrogen balance in hospitalized patients Evaluating protein catabolism Determining nitrogen balance, when used in conjunction with 24-hour fecal nitrogen measurement

**Interpretation:** Urinary nitrogen excretion levels within the normal range are indicative of adequate nutrition. Slightly abnormal excretion rates may be a result of moderate stress or complications such as infection or trauma. Significantly abnormal excretion rates may be associated with severe stress due to multiple traumas, head injury, sepsis, or extensive burns. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g nitrogen/24 hours.
Nitrogen, Total, Feces

**Clinical Information:** Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine; however, fecal nitrogen can account for 30% to 50% of total nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of the protein catabolism and, therefore, urine and fecal nitrogen may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

**Useful For:** Determining nitrogen balance, when used in conjunction with 24-hour urine nitrogen measurement Assessing nutritional status (protein malnutrition) Evaluating protein catabolism

**Interpretation:** Average fecal nitrogen (N) excretion is approximately 1 to 2 g N/24 hours. Significantly abnormal excretion rates, resulting in negative nitrogen balance, may be associated with severe stress due to multiple traumas, head injury, sepsis, or extensive burns. Elevated values above 2.5 g N/24 hours may be consistent with chronic progressive pancreatitis. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g N/24 hours.

**Reference Values:**
<16 years: not established  
> or =16 years: 1-2 g/24 hours

**Clinical References:**
Useful For: Identifying tumors of prostatic origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Nocardia Stain, Varies

Clinical Information: Nocardia species and other aerobic actinomycetes can cause significant disease in immunocompromised patients. Clinical presentations can include, but are not limited to, pneumonia, skin abscess, bacteremia, brain abscess, eye infection, and joint infection. The modified acid-fast stain can detect Nocardia species and other partially-acid fast aerobic actinomycetes directly from clinical specimens.

Useful For: Detection of Nocardia species and other partially-acid fast aerobic actinomycetes in clinical specimens

Interpretation: Patients whose specimens are reported as partially acid-fast positive should be considered potentially infected with Nocardia species or other aerobic actinomycetes, pending definitive diagnosis by molecular methods or culture.

Reference Values: Reported as positive or negative


Non-Gynecologic Direct Smear (Bill Only)

Reference Values: This test is for billing purposes only. This is not an orderable test

Non-Gynecologic ThinPrep (Bill Only)

Reference Values: This test is for billing purposes only. This is not an orderable test

Non-Seasonal Inhalant Allergen Profile, Serum
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to non-seasonal inhalant allergen profile Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Nonalcoholic Steatohepatitis (NASH)-FibroTest, Serum and Plasma**

**Clinical Information:** This test estimates the 3 elementary features of metabolic liver disease: steatosis, activity, and fibrosis. The estimation is made by measuring 10 standard serum biomarkers (gamma-glutamyl transferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, alanine aminotransferase, aspartate aminotransferase, cholesterol, triglycerides and fasting plasma glucose). Results from these tests are combined with the patient's age and gender to estimate hepatic fibrosis (FibroTest), steatosis (SteatoTest 2) and activity (NashTest 2) scores.

**Useful For:** Diagnosis and the follow-up of liver fibrosis, steatosis and inflammation Estimating hepatic fibrosis Assessing inflammation for metabolic diseases Assessing severity of nonalcoholic steatohepatitis (NASH) in patients with nonalcoholic fatty liver disease with steatosis (NAFLD) Assessing steatosis or fatty liver Reassuring patients with steatosis only, without fibrosis Managing patients with severe injuries such as advanced fibrosis and NASH
**Interpretation:** This test provides numeric scores that assess hepatic fibrosis (FibroTest), hepatic inflammation (NashTest 2), and steatosis (SteatoTest 2). Interpretation of the scores is provided in the report. Individual results from the 10 component tests are also provided with institution-specific reference intervals. FibroTest is reported relative to a scale ranging from F0-F4 (F0=no fibrosis, F1=minimal fibrosis, F2=moderate fibrosis, F3=advanced fibrosis, F4=severe fibrosis [cirrhosis]). Fibrosis scores may overlap (eg, F0/F1, F1/F2). NashTest 2 is reported relative to a scale ranging from N0-N3 (N0=no nonalcoholic steatohepatitis: NASH, N1=mild NASH, N2=moderate NASH, N3=severe NASH). Steatosis is reported relative to a scale ranging from S0-S2S3 (S0=no steatosis [<5%], S1=mild steatosis [5-33%], S2/S3=moderate/severe steatosis [34-100%]). A stage of S1 or S2S3 is considered clinically significant.

**Reference Values:**

<table>
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<tr>
<th>NashTest 2 Score</th>
<th>Grade</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.25*</td>
<td>N0</td>
<td>no NASH</td>
</tr>
<tr>
<td>0.25-0.50*</td>
<td>N1</td>
<td>mild NASH</td>
</tr>
<tr>
<td>0.50-0.75*</td>
<td>N2</td>
<td>moderate NASH</td>
</tr>
<tr>
<td>0.75-1.00*</td>
<td>N3</td>
<td>severe NASH *Boundary values can apply to 2 stages based on rounding. For example, a NashTest 2 score of 0.245 will round up to 0.25 and be staged N0. A NashTest 2 score of 0.254 will round down to 0.25 and be staged N2. STEATOTEST 2 INTERPRETATION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SteatoTest 2 Score</th>
<th>Grade</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>S0</td>
<td>no steatosis (</td>
</tr>
<tr>
<td>0.40-0.55*</td>
<td>S1</td>
<td>mild steatosis (3-33%)</td>
</tr>
<tr>
<td>0.55-1.00*</td>
<td>S2</td>
<td>moderate/severe steatosis (34-100%) *Boundary values can apply to 2 stages based on rounding. For example, a SteatoTest 2 score of 0.395 will round up to 0.40 and be staged S0. A SteatoTest 2 score of 0.404 will round down to 0.40 and be staged S1. FIBROTEST INTERPRETATION</td>
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<table>
<thead>
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<th>Interpretation</th>
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</thead>
<tbody>
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<td>No fibrosis</td>
</tr>
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<td>0.21-0.27*</td>
<td>F0-F1</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>0.27-0.31*</td>
<td>F1</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.31-0.48*</td>
<td>F1-F2</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.48-0.58*</td>
<td>F2</td>
<td>Moderate fibrosis</td>
</tr>
<tr>
<td>0.58-0.72*</td>
<td>F3</td>
<td>Advanced fibrosis</td>
</tr>
<tr>
<td>0.72-0.74*</td>
<td>F3-F4</td>
<td>Advanced fibrosis</td>
</tr>
</tbody>
</table>
Severe fibrosis (Cirrhosis) *Boundary values can apply to 2 stages based on rounding. For example, a FibroTest score of 0.305 will round up to 0.31 and be staged F1. A FibroTest score of 0.314 will round down to 0.31 and be staged F1-F2. ALPH A-2-MACROGLOBULIN < or =18 years: 178-495 mg/dL >18 years: 100-280 mg/dL ALANINE AMINOTRANSFERASE (ALT) Males No established reference values > or =1 year: 7-55 U/L Females No established reference values > or =1 year: 7-45 U/L APOLIPOPROTEIN A1 Males No established reference values 2-17 years Low: Borderline low: 115-120 mg/dL Acceptable: >120 mg/dL > or =18 years: > or =120 mg/dL Females No established reference values 2-17 years Low: Borderline low: 115-120 mg/dL Acceptable: >120 mg/dL > or =18 years: > or =140 mg/dL. GAMMA-GLUTAMYLTRANSFERASE (GGT) Males 0-11 months: 12 months-6 years: 7-12 years: 13-17 years: or =18 years: 8-61 U/L Females 0-11 months: 12 months-6 years: 7-12 years: 13-17 years: or =18 years: 5-36 U/L HAPTOGLLOBIN 30-200 mg/dL. BILIRUBIN, TOTAL 0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values. 7-14 days: 15 days to 17 years: < or =1.0 mg/dL > or =18 years: < or =1.2 mg/dL. ASPARTATE AMINOTRANSFERASE (AST) Males 0-11 months: not established 1-13 years: 8-60 U/L > or =14 years: 8-48 U/L Females 0-11 months: not established 1-13 years: 8-50 U/L > or =14 years: 8-43 U/L CHOLESTEROL, TOTAL The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up: TOTAL CHOLESTEROL Desirable: Borderline high: 200-239 mg/dL High: > or =240 mg/dL. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children 2 to 17 years of age: TOTAL CHOLESTEROL Acceptable: Borderline high: 170-199 mg/dL High: > or =200 mg/dL TRIGLYCERIDES The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Non HDL cholesterol) in adults ages 18 and up: TRIGLYCERIDES Normal: Borderline high: 150-199 mg/dL High: 200-499 mg/dL. Very high: > or =500 mg/dL. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2 to 17: TRIGLYCERIDES 2-9 years Acceptable: Borderline high: 75-99 mg/dL High: > or =100 mg/dL 10-17 years Acceptable: Borderline high: 90-129 mg/dL High: > or =130 mg/dL. For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html. GLUCOSE FASTING 0-11 months: not established > or =1 year: 70-100 mg/dL.

**NSRGP 63161**

**Noonan Syndrome and Related Disorders Multi-Gene Panel, Blood**

**Clinical Information:** Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous variants in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a variant in approximately 75% of affected individuals. NS can be sporadic and due to new variants; however, an affected parent can be recognized in 30% to 75% of families. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 variants are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with RAF1 variants, but rarely associated with PTPN11. A number of related disorders exist that have phenotypic overlap with NS and are caused by variants in the same group of genes. PTPN11 and RAF1 variants have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Variants in BRAF, MAP2K1, MAP2K2, and KRAS have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with variants in HRAS. Variation in SHOC2 has been associated with a distinctive phenotype involving features of NS and loose anagen hair. Genes included in the Noonan Syndrome and Related Disorders Multi-Gene Panel Gene Protein Inheritance Disease Association BRAF V-raf-1 murine leukemia viral oncogene homolog b1 AD Noonan/CFC/Costello syndrome CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome KRAS V-KI-RAS Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC NRAS Neuroblastoma ras viral oncogene homolog AD Noonan syndrome PTPN11 Protein-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/LEOPARD syndrome RAF1 V-raf-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome SHOC2 Suppressors of clear, c. Elegantus, homolog of AD Noonan-syndrome like with loose anagen hair SOS1 Son of sevenless, drosophila homolog 1 AD Noonan-syndrome like with loose anagen hair Abbreviations: Autosomal dominant (AD)

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome (NS) or related disorders Establishing a diagnosis of a NS or related disorders, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with
increased risk for disease features allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Normal Transferrin CDG Panel (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**Norovirus PCR, Molecular Detection, Feces**

**Clinical Information:** Noroviruses, previously known as Norwalk-like viruses, are highly contagious RNA viruses that cause acute gastroenteritis (diarrhea, vomiting). Although 6 genogroups of norovirus have been identified, only 3 genogroups (genogroup: G1, G2, and G4) cause disease in humans. Furthermore, the majority of outbreaks have been associated with G1 and G2, with G2 being most common.(1) Noroviruses are transmitted through close, personal contact with an infected individual or via the fecal-oral route, in which the virus becomes ingested in contaminated food or water. These viruses are extremely contagious, with fewer than 20 virions being able to cause disease.(1) Once infected, the incubation period is typically short, between 24 and 72 hours. The onset of symptoms is abrupt, with vomiting and watery nonbloody diarrhea being common. Patients may also experience a low-grade fever, as well as headache and mild body aches.(1) The diagnosis of norovirus infection can often be made on clinical grounds, and symptoms generally resolve in 24 to 48 hours. However, in certain patients, especially those who are immunocompromised or hospitalized, laboratory testing may be indicated for infection control purposes and to limit the use of antibiotics. Testing of diarrheal feces by real-time polymerase chain reaction (PCR) allows for a rapid and sensitive means of detecting and differentiating norovirus G1 and G2 in clinical stool samples.

**Useful For:** Diagnosis of gastrointestinal disease (diarrhea or vomiting) caused by norovirus genogroups 1 and 2 This test should not be used as a test-of-cure.

**Interpretation:** A positive result indicates that nucleic acid (RNA) from norovirus genogroups 1
and/or 2 was present in the clinical specimen. A negative result suggests that nucleic acid (RNA) from norovirus genogroups 1 or 2 was absent in the clinical specimen.

**Reference Values:**


### Northeast Regional Allergen Profile, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to northeast regional allergen profile Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages</td>
</tr>
</tbody>
</table>

Nortriptyline, Serum

**Clinical Information:** Nortriptyline is a tricyclic antidepressant used for treatment of endogenous depression. It also is a metabolite of the antidepressant amitriptyline. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage; amitriptyline is used when the side effect of mild sedation is desirable. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect; blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

**Useful For:** Monitoring nortriptyline concentration during therapy Evaluating potential nortriptyline toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to nortriptyline with serum levels of 70 to 170 ng/mL. Risk of toxicity is increased with nortriptyline levels above 500 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

**Reference Values:**
Therapeutic concentration: 70-170 ng/mL
Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**

NOTCH3 (CADASIL) Sequencing Test

**Clinical Information:** Detects sequence variants in the NOTCH3 gene in patients with CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).

**Reference Values:**
A final report will be attached in MayoAccess.

NR4A3 (9q22.33) Rearrangement, FISH, Tissue

**Clinical Information:** The gene NR4A3 is often altered in patients with extraskeletal myxoid chondrosarcomas (EMC). Rearrangement of the NR4A3 gene region may be involved with up to 4 partner genes as a pathway to EMC. FISH analysis allows for the detection of rearrangement of the NR4A3 gene region.

**Useful For:** Identifying NR4A3 gene rearrangements in patients with extraskeletal myxoid chondrosarcoma (EMC)

**Interpretation:** A positive result with the NR4A3 probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of NR4A3 suggests inactivating structural alterations of the NR4A3 gene region at 9q22.33. A negative result suggests no structural alterations of the locus.
NT-Pro B-Type Natriuretic Peptide, Serum

**Clinical Information:** B-type natriuretic peptide (brain natriuretic peptide: BNP) is a small, ringed peptide secreted by the heart to regulate blood pressure and fluid balance.\(^{(1)}\) This peptide is stored in and secreted predominantly from membrane granules in the heart ventricles in a pro form (proBNP). Once released from the heart in response to ventricle volume expansion or pressure overload, the N-terminal (NT) piece of 76 amino acids (NT-proBNP) is rapidly cleaved by the enzymes corin and furin to release the active 32-amino acid peptide (BNP).\(^{(2)}\) Both BNP and NT-proBNP are markers of atrial and ventricular distension due to increased intracardiac pressure. The New York Heart Association (NYHA) developed a 4-stage functional classification system for congestive heart failure (CHF) based on the severity of the symptoms. Studies have demonstrated that the measured concentrations of circulating BNP and NT-proBNP increase with the severity of CHF based on the NYHA classification.

**Useful For:** Aiding in the diagnosis of congestive heart failure

**Interpretation:** Under 50 years of age: N-terminal pro brain natriuretic peptide (NT-proBNP) values below 300 pg/mL have a 99% negative predictive value for excluding acute congestive heart failure (CHF). A cutoff of 1,200 pg/mL for patients with an estimated glomerular filtration rate (eGFR) below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. NT-proBNP values greater than 450 pg/mL are consistent with CHF in adults under 50 years of age.

NT-proBNP values below 300 pg/mL have a 99% negative predictive value for excluding acute CHF. A cutoff of 1,200 pg/mL for patients with an eGFR below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. A diagnostic NT-proBNP cutoff of 900 pg/mL has been suggested in adults 50 to 75 years of age in the absence of renal failure. Over 75 years of age: NT-proBNP values below 300 pg/mL have a 99% negative predictive value for excluding acute CHF. A cutoff of 1,200 pg/mL for patients with an eGFR below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. A diagnostic NT-proBNP cutoff of 1,800 pg/mL has been suggested in adults over 75 years of age in the absence of renal failure. NT-Pro BNP levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Interpretive Levels for CHF Functional class 5th to 95th Percentile Median I 31-1110 pg/mL II 57-4975 pg/mL II 1223 pg/mL III 77-26,916 pg/mL 3130 pg/mL IV ** ** In a Mayo Clinic study of 75 patients with CHF, only 4 were characterized as Class IV. Accordingly, range and median are not provided.

**Reference Values:**

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**Females**

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79 years: < or =244 pg/mL
80 years: < or =248 pg/mL
81 years: < or =253 pg/mL
82 years: < or =258 pg/mL
> or =83 years: < or =263 pg/mL

diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of
1,256 patients; the International Collaborative of NT-proBNP Study. Eur Heart J. 2006
Feb;27(3):330-337 2. van Kimmenade RRJ, Pinto YM, Bayes-Genis A, Lainchbury JG, Richards AM,
Januzzi JL Jr: Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for
Kimmeneade RRJ, Pinto YM: Amino-terminal pro-B-type natriuretic peptide testing in renal disease. Am J

NTRK Gene Fusion Panel, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that
block the growth and spread of cancer by interfering with specific cell molecules involved in tumor
growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of
specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted
therapies and to minimize treatment costs and therapy-associated risks. Fusions involving the NTRK1,
NTRK2, or NTRK3 genes (ie, NTRK gene fusions) form through intra- and interchromosomal
rearrangements. NTRK gene fusions lead to activation of downstream MAPK, PIK, and STAT3 signaling
pathways and act as oncogenic drivers of multiple types of pediatric and adult solid tumors. In solid
tumors, the presence of an NTRK gene fusion is a biomarker for response to tropomyosin receptor kinase
(TRK) inhibitor therapy. This test assesses for fusions involving the NTRK1, NTRK2, and NTRK3 genes.
The results of this test can be useful in guiding treatment of individuals with advanced solid tumors. See
the NTRK RNA Targeted Gene Fusions table in Special Instructions for details regarding the targeted
gene regions evaluated by this test.

Useful For: Identifying solid tumors that may respond to targeted therapies by simultaneously
assessing for rearrangements involving targeted regions of the NTRK1, NTRK2, and NTRK3 genes
resulting in fusion transcripts This test is not useful for hematologic malignancies.

Interpretation: An interpretive report will be provided.

Reference Values: 
An interpretive report will be provided.

Clinical References: 1. Drilon A, Laetsch TW, Kummar S: Efficacy of Larotrectinib in TRK
10.1056/NEJMoa1714448 2. Cocco E, Scaltriti M, Drilon A: NTRK fusion-positive cancers and TRK

NTX-Telopeptide, Urine

Clinical Information: Human bone is continuously remodeled through a process of
osteoclast-mediated bone formation and resorption. This process can be monitored by measuring serum
and urine markers of bone formation and resorption. Approximately 90% of the organic matrix of bone is
type I collagen, a helical protein that is cross-linked at the N- and C-terminal ends of the molecule. The
amino acid sequences and orientation of the cross-linked alpha 2 N-telopeptide of type 1 collagen make it
a specific marker of human bone resorption. N-terminal telopeptide (NTx) molecules are mobilized from
bone by osteoclasts and subsequently excreted in the urine. Elevated levels of NTx indicate increased
bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and
during fracture healing. The elevations in bone resorption markers and bone formation markers are
typically balanced in these circumstances and of no diagnostic value. By contrast, abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, and bony metastases, as well as various congenital diseases of bone formation and remodeling can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover, usually without increase in bone turnover, is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption and formation markers.

**Useful For:** As an adjunct in the diagnosis of medical conditions associated with increased bone turnover Monitoring effectiveness of antiresorptive therapy in patients treated for osteopenia, osteoporosis, Paget disease, or other metabolic bone disorders

**Interpretation:** Elevated levels of N-terminal telopeptide (NTx) indicate increased bone resorption. Most patients with osteopenia or osteoporosis have low, but unbalanced, bone turnover, with bone resorption dominating over bone formation. While this may result in mild elevations in bone turnover markers in these patients, finding significantly elevated urine NTx levels is atypical. Therefore, if levels are substantially elevated above the young adult reference range (>1.5- to 2-fold), the likelihood of coexisting osteomalacia, or of an alternative diagnosis as described in the Clinical Information section, should be considered. When alternative causes for elevated NTx have been excluded in a patient with osteopenia/osteoporosis, the patient must be considered at increased risk for accelerated progression of osteopenia/osteoporosis. A 30% or greater reduction in this resorption marker 3 to 6 months after initiation of therapy indicates a probably adequate therapeutic response. The Negotiated Rulemaking Committee of Health Care Finance Administration also recommends: "Because of significant specimen to specimen collagen crosslink physiologic variability (15%-20%), current recommendations for appropriate utilization include: 1 or 2 baseline assays from specified urine collections on separate days; followed by a repeat assay about 3 months after starting antiresorptive therapy; followed by a repeat assay in 12 months; thereafter not more than annually, if medically necessary."

**Reference Values:**
All units are reported in nmol bone collagen equivalents (BCE)/mmol creatinine.

**Pediatric**

**Males:**
- Tanner Stage I: 55-508 nmol BCE/mmol creatinine
- Tanner Stage II: 21-423 nmol BCE/mmol creatinine
- Tanner Stage III: 27-462 nmol BCE/mmol creatinine
- Tanner Stage IV: <609 nmol BCE/mmol creatinine
- Tanner Stage V: <240 nmol BCE/mmol creatinine

**Females:**
- Tanner Stage I: 6-662 nmol BCE/mmol creatinine
- Tanner Stage II: 193-514 nmol BCE/mmol creatinine
- Tanner Stage III: 13-632 nmol BCE/mmol creatinine
- Tanner Stage IV: <389 nmol BCE/mmol creatinine
- Tanner Stage V: <132 nmol BCE/mmol creatinine

**Adult (> or =18 years of age)**

**Males:**
- 21-83 nmol BCE/mmol creatinine

**Females:**
- Premenopausal: 17-94 nmol BCE/mmol creatinine
- Postmenopausal: 26-124 nmol BCE/mmol creatinine

**Clinical References:**
Nuclear Magnetic Resonance Lipoprotein Profile, Serum

**Clinical Information:** Low-density lipoprotein particle (LDL-P) concentration is positively associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). LDL-P is heterogeneous and contains many lipids and proteins including phospholipids, triglycerides and cholesterol. LDL cholesterol is a surrogate biomarker of LDL-P. LDL cholesterol (LDL-C) is the historical measure of atherogenic lipid burden. There is a large variance in the relative amount of cholesterol carried by each LDL-P. Consequently, subjects with similar LDL cholesterol values can have markedly different serum concentrations of LDL-P. Multiple studies have shown that serum concentrations of LDL-P more accurately reflect actual risk of ASCVD when LDL cholesterol values are discrepant. High-density lipoprotein particle (HDL-P) concentration is inversely associated with risk of ASCVD. HDL cholesterol is also inversely associated with ASCVD since it is a surrogate marker for HDL-P. Like other lipoproteins, HDL-P is heterogeneous and particles contain highly variable proportions of proteins and lipids including phospholipids, sphingolipids and cholesterol. Several large clinical studies have shown that HDL-P is more significantly associated with ASCVD risk than HDL cholesterol. Furthermore, HDL-P remains significantly associated with ASCVD even among subjects taking cholesterol-lowering medications. HDL-P more accurately reflects actual risk of ASCVD when HDL cholesterol values are discrepant.

**Useful For:** Assessment and management of a patient's risk for atherosclerotic cardiovascular disease

**Interpretation:** Elevated concentrations of low-density lipoprotein particle (LDL-P) are associated with increased risk of atherosclerotic cardiovascular disease. LDL-P is a more accurate indicator of risk when LDL cholesterol (LDL-C) is discordantly low. Lower concentrations of high-density lipoprotein particle (HDL-P) are associated with increased risk of atherosclerotic cardiovascular disease.

**Reference Values:**

> or = 18 years:

**LDL Particles:**
- Desirable: < 1,000 nmol/L
- Above Desirable: 1,000-1,299 nmol/L
- Borderline high: 1,300-1,599 nmol/L
- High: 1,600-2,000 nmol/L
- Very high: > or = 2,000 nmol/L

**HDL Particles:**
- Male: > 30 mcmol/L
- Female: > 35 mcmol/L

**LDL Cholesterol (NMR):**
- Desirable: < 100 mg/dL
- Above Desirable: 100-129 mg/dL
- Borderline high: 130-159 mg/dL
- High: 160-189 mg/dL
- Very high: > or = 190 mg/dL

Reference values have not been established for patients who are < 18 years of age.

**Clinical References:** 1. Mora S, Glynn RJ, Ridker PM: High-Density Lipoprotein Cholesterol, Size,
NPM1Q

**Nucleophosmin (NPM1) Mutation Analysis, Varies**

**Clinical Information:** Acute myeloid leukemia (AML) is a genetically heterogeneous group of neoplasms. While cytogenetic aberrations detected at the time of diagnosis are the most used prognostic feature, approximately 50% of AML cases show a normal karyotype, which is considered an intermediate-risk feature. Within this group, FLT3 variants are considered indicators of poor prognosis. However, in the absence of a FLT3 variant, the presence of a nucleophosmin (NPM1) variant is associated with a more favorable prognosis. A NPM1 alteration is a common finding in de novo AML (25%-30% of cases) and consists of small insertion (typically 4 base pair) or insertion/deletion events involving exon 12. Three variants are highly recurrent, termed types A, B, and D and together account for approximately 90% of NPM1 alterations in de novo AML. Thus, in patients with newly diagnosed AML, those with normal karyotype, no FLT3 variant, and a NPM1 alteration are considered to have a better prognosis than patients in the same group with neoplasms lacking a NPM1 alteration. Furthermore, the presence of a NPM1 alteration serves as a sensitive marker for evaluating minimal disease and therapeutic response following treatment.

**Useful For:** As a prognostic indicator in patients with newly diagnosed acute myelogenous leukemia with normal karyotype and no FLT3 mutation and as a leukemia-specific marker of minimal residual disease

**Interpretation:** The assay incorporates 2 parts: a qualitative screen for exon 12 nucleophosmin (NPM1) alterations, and a quantitative reverse transcription polymerase chain reaction (RT-PCR) to determine the copy number of NPM1 transcripts (relative to ABL1 reference mRNA). This strategy will allow for identification of the NPM1 alteration at diagnosis, as well as a high sensitivity method to monitor patients who are post-therapy for minimal residual disease (MRD). Results will therefore be interpreted with integration of the quantitative and qualitative test results in the context of NPM1 alteration type identified at the time of AML diagnosis if available. Because the quantitative RT-PCR component only reliably detects and quantifies the 3 most common variant types (A, B, D), there is a very small possibility that the qualitative assay may indicate the presence of NPM1 alteration, but the quantitative assay will be (falsely) negative. In patients with newly diagnosed acute myeloid leukemia, a normal karyotype, and no FLT3 variant, the presence of NPM1 alteration is an indicator of a more favorable prognosis. Similarly, following chemotherapy, the presence, relative quantity and trend of change of NPM1 mRNA transcript is associated with risk of disease relapse.

**Reference Values:** An interpretive report will be provided.

NUT Immunostain, Technical Component Only

Clinical Information: Nuclear protein in testis (NUT) is normally confined to the germ cells of the testis and ovary. A recently recognized cancer is NUT midline carcinoma (NMC), defined by the presence of chromosomal rearrangements involving the NUT gene on chromosome 15q14. NMCs are aggressive and highly lethal carcinomas, and are very difficult to discern from other poorly differentiated carcinomas by morphology alone.

Useful For: Aiding in the diagnosis of nuclear protein in testis (NUT) midline carcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


NUT1F (15q14) Rearrangement, FISH, Tissue

Clinical Information: Nuclear protein in testis (NUT) midline carcinomas (NMC) are rare aggressive tumors with rapid onset. Although NMC has been described in several anatomic sites, it is commonly observed in the head, neck, or thorax. These tumors are poorly differentiated and defined by rearrangement of the NUTM1 gene on chromosome 15q14. In the majority of cases, NUTM1 is rearranged in an apparently balanced translocation with the BRD4 gene on chromosome 19p13.1; however, other partners for NUTM1 rearrangement have been reported. NUTM1 rearrangement has not been identified in other midline malignancies. Therefore, a separation of NUTM1, in the proper clinical and histologic context, is diagnostic for NMC and can be confirmed by fluorescence in situ hybridization with NUT break-apart probes.

Useful For: Identifying NUTM1 gene rearrangements in patients with nuclear protein in testis midline carcinoma to aid in confirming or excluding the diagnosis

Interpretation: The presence of NUTM1 rearrangement confirms the diagnosis of nuclear protein in testis midline carcinomas (NMC) in the proper clinical and histologic context. The absence of NUTM1 rearrangement rules out the diagnosis of NMC in the proper clinical and histologic context. A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe
A positive result suggests rearrangement of the NUTM1 locus which, in conjunction with the proper clinical and histologic features, is diagnostic of NMC. A negative result suggests no rearrangement of the NUTM1 gene region at 15q14. A confirmed diagnosis of NMC results in specific clinical management that may be distinct from the management of other carcinomas.

Reference Values:
An interpretive report will be provided.

Clinical References:

NMEG
82497

Nutmeg, IgE, Serum
Clinical Information:
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effectors cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For:
Establishing the diagnosis of an allergy to nutmeg
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens:
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation:
Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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Reference values apply to all ages.

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**NUTSP 31771**

**Nuts Allergen Profile, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to nuts Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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For Allergen PEAN:

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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
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Reference values apply to all ages.
Nuts and Grains Panel IgG

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Oak Live (Quercus virginiana) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 ≤ IgE < 0.34
Equivocal/Borderline 1 0.35 ≤ IgE < 0.69 Low Positive 2 0.70 ≤ IgE < 3.49 Moderate Positive 3 3.50 ≤ IgE < 17.49 High Positive 4 17.50 ≤ IgE < 49.99 Very High Positive 5 ≥ 50.00 Very High Positive

**Reference Values:**
<0.35 kU/L

Oak Red (Quercus rubra) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 ≤ IgE < 0.69 Low Positive 2 0.70 ≤ IgE < 3.49 Moderate Positive 3 3.50 ≤ IgE < 17.49 High Positive 4 17.50 ≤ IgE < 49.99 Very High Positive 5 ≥ 50.00 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Oak, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to oak Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the
specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Oat IgG**

**FOATG 57576**

**Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Oat, IgE, Serum**

**OATS 82688**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to oat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic
reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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Reference values apply to all ages.


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**OCT2 Immunostain, Technical Component Only**

**Clinical Information:** OCT-2 is a transcription factor that binds to the octamer motif of the immunoglobulin gene promoter, recruits the coactivator BOB.1, and activates immunoglobulin gene transcription. OCT-2 is variably expressed in germinal center B cells, weakly expressed in mantle zone B cells, and weakly to moderately expressed in plasma cells. The protein is localized to the nuclear compartment. Expression of BOB.1, OCT-2, and PU.1 transcription factors are often down regulated in classical Hodgkin lymphoma. OCT-2 is overexpressed in lymphocyte-predominant (LP) cells of nodular LP Hodgkin lymphoma. These properties can be useful in the diagnosis of lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

OCT4

OCT3/4 Immunostain, Technical Component Only

Clinical Information: Octamer-binding transcription factor 3/4 (OCT4), also known as POU5F1, is a transcription factor expressed by embryonal stem cells and germ cells. Staining for OCT4 can aid in the diagnosis of testicular or ovarian germ cell tumors; it is highly specific for germ cell neoplasia, especially seminomas. Alternative splicing produces 2 mRNA variants from the POU5F1 gene, originally named OCT3A and OCT3B, thus the OCT3/4 name.

Useful For: Aids in the identification of germ cell tumors

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


OCTO

Octopus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to octopus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

**Olanzapine (Zyprexa)**

**Reference Values:**
Reference Range: 10.0–80.0 ng/mL

Expected steady state concentrations in patients on recommended daily dosages:
- 10.0–80.0 ng/mL
- Plasma concentrations of olanzapine greater than 9.0 ng/mL have been associated with therapeutic effect.

Toxic range has not been established.

**OLIG2 Immunostain, Technical Component Only**

**Clinical Information:** Oligodendrocyte transcription factor 2 (OLIG2) is a transcription factor that participates in oligodendrocyte and motor neuron differentiation. During embryogenesis OLIG2 promotes the growth of motor neuron progenitor cells. OLIG2 expression decreases upon further neuronal differentiation. OLIG2 is also involved in oligodendrocyte differentiation where expression remains present in mature glial cells. In gliomas, OLIG2 represses the p53 tumor suppressor pathway, thereby contributing to glioma progression.

**Useful For:** Distinguishing gliomas from neurocytomas and ependymomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Clinical Information:** The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include kappa free light chains in the cerebrospinal fluid (CSF) and CSF oligoclonal band (OCB) detection. Abnormal CSF OCB patterns have been reported in 70% to 80% of MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases, and therefore, this assay is not specific for MS.

**Useful For:** Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings Determining number of serum oligoclonal bands in order to calculate the number of cerebrospinal fluid-specific bands present

**Interpretation:** When the oligoclonal band assay detects 2 or more unique IgG bands in the cerebrospinal fluid (CSF), the result is positive. CSF is used in the diagnosis of multiple sclerosis (MS) by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria. These findings, however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation recommended.

**Reference Values:**
Only orderable as part of a profile. For more information see:
- OLIG / Oligoclonal Banding, Serum and Spinal Fluid
- MSP3 / Multiple Sclerosis (MS) Profile

**Clinical References:**
Oligoclonal Banding, Spinal Fluid

**Clinical Information:** The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the cerebrospinal fluid (CSF) IgG index and CSF oligoclonal band (OCB) detection. Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases and, therefore, this assay is not specific for MS.

**Useful For:** Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings

**Interpretation:** When the oligoclonal band assay detects 2 or more unique IgG bands in the cerebrospinal fluid (CSF), the result is positive. CSF is used in the diagnosis of multiple sclerosis (MS) by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria. These findings however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation recommended.

**Reference Values:**
Only orderable as part of a profile. For more information, see:
- OLIG / Oligoclonal Banding, Serum and Spinal Fluid
- MSP3 / Multiple Sclerosis (MS) Profile, Serum and Spinal Fluid

Cerebrospinal fluid Oligoclonal Bands Interpretation: <2 bands

**Clinical References:**
2. Fortini AS, Sanders EL, Weinschenker BG, Katzmann JA: Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis, isoelectric focusing with the IgG immunoblotting compared with high resolution agarose gel electrophoresis and cerebrospinal fluid IgG index. Am J Clin Pathol. 2003;120:672-675
Oligosaccharide Screen, Random, Urine

Clinical Information: The oligosaccharidoses (glycoproteinoses) are a subset of lysosomal storage disorders (LSD) caused by the deficiency of any one of the lysosomal enzymes involved in the degradation of complex oligosaccharide chains. They are characterized by the abnormal accumulation of incompletely degraded oligosaccharides in cells and tissues and the corresponding increase of related free oligosaccharides in the urine. Clinical diagnosis can be difficult due to the similarity of clinical features across disorders and their variable severity. Clinical features can include bone abnormalities, coarse facial features, corneal cloudiness, organomegaly, muscle weakness, hypotonia, developmental delay, and ataxia. Age of onset ranges from early infancy to adult and can even present prenatally. The oligosaccharidoses and other storage disorders detected by this test include alpha-mannosidosis, beta-mannosidosis, aspartylglucosaminuria, fucosidosis, Schindler disease, GM1 gangliosidosis, Sandhoff disease, sialidosis, galactosialidosis, mucolipidosis types II and III, mucopolysaccharidosis IVA (Morquio A), mucopolysaccharidosis IVB (Morquio B), and Pompe disease (see table). Additional conditions that may be picked up by this test include other mucopolysaccharidoses, Gaucher disease, Krabbe disease, and some congenital disorders of glycosylation (PMM2, NGLY1, MOGS, ALG1, MAN1B1). Conditions identifiable by method Disorder Onset Gene Enzyme deficiency Worldwide incidence Alpha-mannosidosis Prenatal (type III) Infant (type I) Juvenile/Adult (type II) MAN2B1 Alpha-mannosidase 1:500,000 Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course. Prenatal onset (type III) manifests as prenatal loss or early death from progressive neurodegeneration. Infantile onset (type I) is characterized by rapidly progressive mental retardation, hepatosplenomegaly, and severe dysostosis multiplex. Type II is milder and slower progressing with survival into adulthood. Beta-mannosidosis Infant to juvenile MANBA Beta-mannosidase <100 patients described Phenotype: clinical features vary in severity and may include intellectual disability, respiratory infections, hearing loss, hypotonia, peripheral neuropathy, and behavioral issues. Aspartylglucosaminuria Early childhood AGA Aspartylglucosaminidase 1:2,000,000 higher incidence in Finland approx 1:17,000 Phenotype: normal appearing at birth followed by progressive neurodegeneration at 2-4 years, frequent respiratory infections, coarse features, thick calvarium, and osteoporosis. Slowly progressive mental decline into adulthood. Alpha-fucosidosis Infant to early childhood FUCA1 Alpha-fucosidase <100 patients described Phenotype: continuum within a wide spectrum of severity; clinical features include neurodegeneration, coarse facial features, growth delay, recurrent infections, dysostosis multiplex, angiokeratoma, and elevated sweat chloride. Schindler disease Infant (type I) Early childhood (type III) Adult (type II) NAGA Alpha-N-acetyl-galactosaminidase <30 patients described Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course; infantile onset (type I) is characterized by rapidly progressive neurodegeneration. Type II is adult onset characterized by angiokeratoma and mild cognitive impairment, and type III is an intermediate and variable form ranging from seizures and psychomotor delay to milder autistic features. GM1 gangliosidosis Infant (type I) Late infantile/juvenile (type II) Adult (type III) GLB1 Beta-galactosidase (Beta-Gal) 1:200,000 Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course; infantile onset (type I) is characterized by early developmental delay/arrest followed by progressive neurodegeneration, skeletal dysplasia, facial coarseness, hepatosplenomegaly, and macular cherry red spot. Later onset forms (types II and III) are milder and observed as progressive neurologic disease and vertebral dysplasia. Adult onset presents mainly with dystonia. GM2 gangliosidosis variant 0 (Sandhoff disease) Early infancy to juvenile or adult HEXB Beta-hexosaminidase A and B 1:400,000 Phenotype: infantile onset is characterized by rapidly progressive neurodegeneration, exaggerated startle reflex, “cherry red spot”. Milder later-adult onset forms of the disease exist presenting with neurological problems such as ataxia, dystonia, spinocerebellar degeneration, and behavior changes. Sialidosis (ML I) Early adulthood (type I) Earlier for congenital, infantile, and juvenile forms (type II) NEU1 Alpha-neuraminidase (Neu) <30 patients described Phenotype: continuum of clinical features ranging from severe disease (type II) to a milder and more slowly progressive course (type I). Clinical features range from early developmental delay, coarse facial features, short stature, dysostosis multiplex, and hepatosplenomegaly to late onset cherry-red spot myoclonus syndrome. Seizures, hyperreflexia, and ataxia have been reported in more than 50% of later onset patients. A congenital form of the disease has been reported in which patients present with fetal hydrops or neonatal ascites. Galactosialidosis Early infancy, late infancy or early adult CTSA Cathepsin A causing secondary deficiencies in Beta-Gal and Neu <30 patients described Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly
progressive course; clinical features of the early infantile type include fetal hydrops, edema, ascites, visceromegaly, dysostosis multiplex, coarse facies, and cherry red spot. The majority of patients have milder presentations, which include ataxia, myoclonus, angiookeratoma, cognitive and neurologic decline.

Mucolipidosis II-alpha/-beta (I-cell) Mucolipidosis III-alpha/-beta and III-gamma (pseudo-Hurler Polydystrophy) Early infancy Early childhood, may live well into adulthood GNPTAB(alpha/beta) GNPTG (gamma) N-acetylglucosaminyl-1-phosphotransferase deficiency causing secondary intracellular deficiency of multiple enzyme activities 1:300,000 Phenotype: I-cell resembles Hurler with short stature and skeletal anomalies, but presents earlier, is more severe, and can include cardiomyopathy and coronary artery disease. Pseudo-Hurler polydystrophy is milder and later presenting. Mucopolysaccharidosis IVB (Morquio B) Infancy to adult GLB1 Beta-Gal 1:75,000 N. Ireland 1:640,000 W. Australia Phenotype: progressive condition that largely affects the skeletal system. Features include short-trunk dwarfism, skeletal (spondyloepiphyseal) dysplasia, fine corneal deposits, and preservation of intelligence. Pompe disease (glycogen storage disease type II) Early infancy Late onset (childhood-adult) GAA Alpha-glucosidase 1:40,000 Phenotype: infantile onset is characterized by prominent cardiomegaly, hepatomegaly, hypotonia, and weakness. Later onset forms present with proximal muscle weakness and respiratory insufficiency.

Useful For: Screening for selected oligosaccharidoses

Interpretation: This is a screening test; not all oligosaccharidoses are detected. The resulting excretion profile may be characteristic of a specific disorder; however, abnormal results require confirmation by enzyme assay or molecular genetic testing. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of results and significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional confirmatory studies (enzyme assay, molecular genetic analysis).

Reference Values: An interpretive report will be provided.


Olive Black IgG

Interpretation:

Reference Values: Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

OLIV

Olive Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to olive tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Olive-Food, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to olive-food Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies

Clinical Information: Next-generation sequencing (NGS) is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many myeloid neoplasms lack a clonal cytogenetic finding at diagnosis (normal karyotype) but can be diagnosed and classified according to the gene mutation profile. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and sometimes therapeutic information for the managing physicians.

Useful For: Evaluation of hematologic neoplasms, specifically of myeloid origin (eg, acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative neoplasm, myelodysplastic/myeloproliferative neoplasm) at the time of diagnosis or possibly disease relapse, to help determine diagnostic classification and provide prognostic or therapeutic information for clinical management. Determine the presence of new clinically important gene mutation changes at relapse.

Interpretation: Mutations (gene alterations) identified, if present, using human reference genome build GRCh37 (hg19). An interpretive report will be provided. If this test is ordered in the setting of erythrocytosis and suspicion of polycythemia vera, interpretation requires correlation with a concurrent or recent prior bone marrow evaluation.

Reference Values: An interpretive report will be provided.

Onion IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Onion, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to onion Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson, MR
**Clinical Information:** Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds(1): -Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect.(2) Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation. -Morphine is an opioid receptor agonist that is used for major pain analgesia.(2) It has been shown to distribute widely into many fetal tissues,(4) and has been detected in meconium. -Hydrocodone is a semisynthetic analog derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain.(2) Hydrocodone undergoes O-demethylation in vivo, forming hydromorphone. -Hydromorphone, a semisynthetic derivative of morphine, is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine.(2) -Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphine.(2) -Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain.(2) -Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monoacetylmorphine (6-MAM), which is further hydrolyzed to morphine.(2) Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of maternal prenatal opiate/opioid use up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of any of the following opiates (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) at > or =50 ng/g or 6-monoacetylmorphine at > or =10 ng/g indicates the newborn was exposed to opiates/opioids during gestation.

**Reference Values:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative</strong></td>
<td>Positive at &gt; or =50 ng/mL for codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone</td>
</tr>
<tr>
<td></td>
<td>Positive at &gt; or =10 ng/mL for 6-monoacetylmorphine</td>
</tr>
</tbody>
</table>

Cutoff concentrations:
- Codeine by LC-MS/MS: 50 ng/mL
- Hydrocodone by LC-MS/MS: 50 ng/mL
- Hydromorphone by LC-MS/MS: 50 ng/mL
- Morphine by LC-MS/MS: 50 ng/mL
Oxycodone by LC-MS/MS: 50 ng/mL
Oxymorphine by LC-MS/MS: 50 ng/mL


Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds: -Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect. Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation. -Morphine is an opioid receptor agonist that is used for major pain analgesia. -Hydrocodone is a semisynthetic analgesic derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain. -Hydromorphone is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine. -Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphone. -Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain. -Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monoacetlymorphine (6-MAM), which is further hydrolyzed to morphine. Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive suckling, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

Useful For: Detection of maternal prenatal opiate/opioid use up to 5 months before birth

Interpretation: The presence of any of the following opiates (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) at 50 ng/g or greater or 6-monoacetlymorphine at 10 ng/g or greater indicates the newborn was exposed to opiates/opioids during gestation.

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**
- Codeine by LC-MS/MS: 50 ng/g
- Hydrocodone by LC-MS/MS: 50 ng/g
- Hydromorphone by LC-MS/MS: 50 ng/g
- Morphine by LC-MS/MS: 50 ng/g
- Oxycodone by LC-MS/MS: 50 ng/g
- Oxymorphone by LC-MS/MS: 50 ng/g

**Clinical References:**

**Clinical Information:**
Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours; and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, *Papaver somniferum*. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2,000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. Dihydrocodeine is a semisynthetic narcotic analgesic prepared by the hydrogenation of codeine. It is also a minor metabolite of hydrocodone. It is metabolized to dihydromorphone and has a half-life of 3.4 to 4.5 hours. Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphine and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. Naloxone is a synthetic narcotic antagonist and used for partial or complete reversal of opioid depression induced by natural or synthetic opioids. It has also been incorporated into oral tablets of opioids to discourage abuse. The duration of action is dependent on the dose and route of administration. The half-life in adults is approximately 30 to 81 minutes. The detection interval for the opiates is generally 2 to 3 days after last ingestion. Chain of custody is a record of the disposition of a specimen to document who collected it,
who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, noroxycodone, noroxymorphone, norhydrocodone, dihydrocodeine, and naloxone in urine. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**
- Negative
- Cutoff concentrations

**IMMUNOASSAY SCREEN**

300 ng/mL

Codeine by LC-MS/MS: 25 ng/mL
Dihydrocodeine by LC-MS/MS: 25 ng/mL
Hydrocodone by LC-MS/MS: 25 ng/mL
Norhydrocodone by LC-MS/MS: 25 ng/mL
Hydromorphone by LC-MS/MS: 25 ng/mL
Oxycodone by LC-MS/MS: 25 ng/mL
Noroxycodone by LC-MS/MS: 25 ng/mL
Oxymorphone by LC-MS/MS: 25 ng/mL
Noroxymorphone by LC-MS/MS: 25 ng/mL
Naloxone by LC-MS/MS: 25 ng/mL
Morphine by LC-MS/MS: 25 ng/mL

**Clinical References:**

**OPATU 8473 Opiates Confirmation, Random, Urine**

**Clinical Information:** Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours, and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2,000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of
parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone greater than 100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. Dihydrocodeine is a semisynthetic narcotic analgesic prepared by the hydrogenation of codeine. It is also a minor metabolite of hydrocodone. It is metabolized to dihydromorphine and has a half-life of 3.4 to 4.5 hours. Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides, and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. Naloxone is a synthetic narcotic antagonist and used for partial or complete reversal of opioid depression induced by natural or synthetic opioids. It has also been incorporated into oral tablets of opioids to discourage abuse. The duration of action is dependent on the dose and route of administration. The half-life in adults is approximately 30 to 81 minutes. The detection interval for opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, noroxycodone, noroxymorphone, norhydrocodone, dihydrocodeine, and naloxone in urine

**Interpretation:** This test reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

**Negative**

Cutoff concentrations

- Codeine by LC-MS/MS: 25 ng/mL
- Dihydrocodeine by LC-MS/MS: 25 ng/mL
- Hydrocodone by LC-MS/MS: 25 ng/mL
- Norhydrocodone by LC-MS/MS: 25 ng/mL
- Hydromorphone by LC-MS/MS: 25 ng/mL
- Oxycodone by LC-MS/MS: 25 ng/mL
- Noroxycodone by LC-MS/MS: 25 ng/mL
- Oxymorphone by LC-MS/MS: 25 ng/mL
- Noroxymorphone by LC-MS/MS: 25 ng/mL
- Naloxone by LC-MS/MS: 25 ng/mL
- Morphine by LC-MS/MS: 25 ng/mL

**Clinical References:**

oxymorphone. All drugs covered and the non-glucuronidated (free) form.

Positive cutoff: 2 ng/mL

For medical purposes only; not valid for forensic use.

**Orange IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Orange Roughy IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**Orange, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to orange Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Clinical References:** Orchard Grass, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to orchard grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Clinical References: Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry’s Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
Oregano IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Oregano, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to oregano Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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<td>3</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or &gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

ORXNA

604230

Orexin-A/Hypocretin-1, Spinal Fluid

Clinical Information: Narcolepsy affects 0.02% to 0.05% of the population and the onset of symptoms often occurs in adolescence. Orexin (also known as orexin-A or hypocretin-1) is a neuropeptide produced in the hypothalamus and is involved in the sleep/wake cycle in humans. Impairment of orexin production and orexin-modulated neurotransmission is associated with narcolepsy with cataplexy (episodes of muscle weakness in response to emotional stimuli). An abnormally low concentration of orexin-A/hypocretin-1 in cerebrospinal fluid (CSF) is indicative of what is termed type 1 narcolepsy. Survey of the literature reveals that approximately 85% to 95% of randomly selected individuals with type 1 narcolepsy and typical cataplexy, exhibit low (<110 pg/mL) CSF orexin (hypocretin-1) concentrations.(1) In one large study, the sensitivity of this cutoff was found to be 87% with a specificity of 99%. (2) Orexin deficiency and type 1 narcolepsy are closely associated with HLA complex DQB1*0602. It is estimated that only 1 in 500 HLA DQB1*0602-negative individuals exhibit low CSF orexin concentrations. CSF concentrations have been found to almost always be above 200 pg/mL in healthy individuals and those with non-type 1-narcoleptic sleep disorders such as narcolepsy type 2 and idiopathic hypersomnia.

Useful For: Aiding in the diagnosis and differentiation of type 1 narcolepsy from other causes of hypersomnolence. This assay is not intended for use as a screening test.

Interpretation: The diagnostic criteria for type 1 narcolepsy in the International Classification of Sleep Disorders (3) include the presence of hypersomnia, cataplexy (episodes of muscle weakness in response to emotional stimuli) and/or measured cerebrospinal fluid (CSF) orexin (hypocretin-1) concentrations less than or equal to 110 pg/mL. Orexin (hypocretin-1) CSF concentrations have been classified into 3 categories in the literature. They include low (< or =110 pg/mL), which is indicative of type 1 narcolepsy; intermediate (ranges between 111-200 pg/mL); and normal (>200 pg/mL). Previous studies have shown that 106 of 113 patients with clinically defined type 1 narcolepsy exhibited low (<110 pg/mL) orexin concentrations. In another study, all 48 healthy individuals exhibited orexin (hypocretin-1) CSF concentrations above 200 pg/mL. In the periodic hypersomnia disorder of Kleine-Levin syndrome, the CSF orexin levels may be low during the sleepy periods, with return to normal when individuals are not sleepy.

Reference Values:
Normal individuals should be >200 pg/mL

Previous literature has defined CSF orexin-A/hypocretin-1 concentrations of < or =110 pg/mL as being consistent with narcolepsy type 1-(Mignot E: Arch Neurol 2002;59:1553-1562). Concentrations between 111 to 200 pg/mL are considered intermediate and have limited diagnostic utility for narcolepsy, as they may be representative of other neurological disorders. Concentrations of >200 pg/mL are considered normal.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1897
Organic Acids Screen, Random, Urine

**Clinical Information:** Organic acids occur as physiologic intermediates in a variety of metabolic pathways. Organic acidurias are a group of disorders in which one or more of these pathways are blocked, resulting in a deficiency of normal products and an abnormal accumulation of intermediate metabolites (organic acids) in the body. These excess metabolites are excreted in the urine. The incidence of individual inborn errors of organic acid metabolism varies from 1 in 10,000 to greater than 1 in 1,000,000 live births. Collectively, their incidence approximates 1 in 3000 live births. This estimate, however, does not include other inborn errors of metabolism (ie, amino acid disorders, urea cycle disorders, congenital lactic acidemias) for which diagnosis and monitoring may also require organic acid analysis. If all possible disease entities were included, the incidence of conditions where informative organic acid profiles could be detected in urine is likely to approach 1 in 1000 live births. Organic acidurias typically present with either an acute life-threatening illness in early infancy or unexplained developmental delay with intercurrent episodes of metabolic decompensations in later childhood. A situation of severe and persistent metabolic acidosis of unexplained origin, elevated anion gap, and severe neurologic manifestations, such as seizures, should be considered strong diagnostic indicators of one of these diseases. The presence of ketonuria, occasionally massive, provides an important clue toward the recognition of disorders, especially in the neonatal period. Hyperammonemia, hypoglycemia, and lactic acidemia are frequent findings, especially during acute episodes of metabolic decompensations.

**Useful For:** Diagnosis of inborn errors of metabolism

**Interpretation:** When no significant abnormalities are detected, the organic acid analysis is reported and interpreted in qualitative terms only. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Organism Referred for Identification, Aerobic Bacteria

**Clinical Information:** Organisms are referred to confirm identification or when the identity is unknown. This may provide helpful information regarding the significance of the organism, its role in the disease process, and its possible origin. Techniques employed may include conventional biochemical analysis, commercial identification strips or panels, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry or sequencing nucleic acid of the 16S ribosomal RNA (rRNA) gene.

**Useful For:** Identification of pure isolates of aerobic bacteria Differentiation of members of the Staphylococcus aureus complex (S aureus, S argenteus, S schweitzeri)

**Interpretation:** Genus and species are reported on aerobic bacterial isolates, whenever possible. Bacillus species will be reported out as “Large spore-forming aerobic gram-positive Bacillus, not Bacillus cereus or Bacillus anthracis,” unless species identification is specifically requested on the request form.

**Reference Values:**
Identification of organism

**Clinical References:**
**ANIDE 8114**

Organism Referred for Identification, Anaerobic Bacteria

**Clinical Information:** Anaerobic bacteria are the greatest component of the human body's normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts. Their presence is important in promoting vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. Anaerobes generally are of low pathogenicity, but may possess virulence factors such as endotoxin or polysaccharide capsules or produce extracellular toxins. Disease occurs when a large inoculum develops in an area lacking oxygen or with a poor blood supply. Typical anaerobic infections include peritonitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema, lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Many Bacteroides produce beta-lactamase and are resistant to penicillins and cephalosporins. Imipenem, metronidazole, and clindamycin are effective agents, although resistance to clindamycin is increasing.

**Useful For:** Identification of anaerobic bacteria involved in human infections

**Interpretation:** Isolation of anaerobes in significant numbers from well-collected specimens from blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with the identified organism.

**Reference Values:**
Identification of organism

**Clinical References:**

**FOGPM 75384**

Organophosphate Pesticide Metabolites, Urine

**Reference Values:**
Reporting limit determined each analysis.

- **Creatinine (mg/L):**
  - U.S. Population (10th - 90th percentiles, median)
    - All participants:
      - 335 - 2370 mg/L, median: 1180 (n=22,245)
    - Males:
      - 495 - 2540 mg/L, median: 1370 (n=10,610)
    - Females:
      - 273 - 2170 mg/L, median 994 (n=11,635)

- **Dimethylphosphate (DMP):** None Detected ng/mL
- **Dimethylthiophosphate (DMTP):** None Detected ng/mL
- **Dimethyldithiophosphate (DMDTP):** None Detected ng/mL
- **Sum of Dimethyl Alkyl Phosphates (DMAP):** None Detected nmol/L

CDC/NHANES 2007 - 2008 U.S. Population:
- Generally less than 580 nmol/L

- **Sum of Dimethyl Alkyl Phosphates (DMAP), (Creatinine Corrected):** None Detected nmol/g Creatinine

CDC/NHANES 2007 - 2008 U.S. Population:
- Generally less than 550 nmol/g Creatinine

- **Diethylphosphate (DEP):** None Detected ng/mL
Diethylthiophosphate (DETP): None Detected ng/mL

Diethyldithiophosphate (DEDTP): None Detected ng/mL

Sum of Diethyl Alkyl Phosphates (DEAP): None Detected nmol/L
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 130 nmol/L

Sum of Diethyl Alkyl Phosphates (DEAP) (Creatinine Corrected): None Detected nmol/g Creat
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 130 nmol/g Creatinine

Total Dialkyl Phosphates (DAP): None Detected nmol/L
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 710 nmol/L

Total Dialkyl Phosphates (DAP) (Creatinine Corrected): None Detected nmol/g Creat
CDC/NHANES 2007 - 2008 U.S. Population:

**OROT 8905**

**Orotic Acid, Random, Urine**

**Clinical Information:** Urinary excretion of orotic acid, an intermediate in pyrimidine biosynthesis, is increased in many urea cycle disorders and in a number of other disorders involving the metabolism of arginine. The determination of orotic acid can be useful to distinguish between various causes of elevated ammonia (hyperammonemia). Hyperammonemia is characteristic of all urea cycle disorders, but orotic acid is elevated in only some, including ornithine transcarbamylase (OTC) deficiency, citrullinemia, and argininosuccinic aciduria. Orotic acid is also elevated in the transport defects of dibasic amino acids (lysinuric protein intolerance and hyperornithinemia, hyperammonemia, and homocitrullinuria [HHH] syndrome) and is greatly elevated in patients with hereditary orotic aciduria (uridine monophosphate synthase [UMPS] deficiency). OTC deficiency is an X-linked urea cycle disorder that affects both male patients and, due to random X-inactivation, female patients. It is thought to be the most common urea cycle disorder with an estimated incidence of 1:56,000. In OTC deficiency, carbamoyl phosphate accumulates and is alternatively metabolized to orotic acid. Allopurinol inhibits orotidine monophosphate decarboxylase and, when given to OTC carriers (who may have normal orotic acid excretion), can cause increased excretion of orotic acid. When orotic acid is measured after a protein load or administration of allopurinol, its excretion is a very sensitive indicator of OTC activity. A carefully monitored allopurinol challenge followed by several determinations of a patient's orotic acid excretion can be useful to identify OTC carriers, as approximately 20% of OTC variant are not detectable by current molecular genetic testing methods.

**Useful For:** Evaluation of the differential diagnosis of hyperammonemia and hereditary orotic aciduria
Sensitive indicator of ornithine transcarbamylase (OTC) activity after administration of allopurinol or a protein load to identify OTC carriers

**Interpretation:** The value for the orotic acid concentration is reported. The interpretation of the result must be correlated with clinical and other laboratory findings.

**Reference Values:**
- <2 weeks: 1.4-5.3 mmol/mol creatinine
- 2 weeks-1 year: 1.0-3.2 mmol/mol creatinine
- 2-10 years: 0.5-3.3 mmol/mol creatinine
- > or =11 years: 0.4-1.2 mmol/mol creatinine


**Orris Root (Iris florentina) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Orthostatic Protein, Timed Collection, Urine**

**Clinical Information:** Orthostatic proteinuria refers to the development of increased proteinuria that develops only when the person is upright and resolves when recumbent or supine. This condition is usually seen in children, adolescents, or young adults, and accounts for the majority of cases of proteinuria in childhood. Orthostatic proteinuria usually does not indicate significant underlying renal pathology, and is usually not associated with other urine abnormalities such as hypoalbuminemia, hematuria, red blood cell casts, fatty casts, etc. Orthostatic proteinuria typically resolves over time. This test characterizes this condition by obtaining 2 urine collections within a 24-hour time frame, one collection obtained while the person is recumbent or supine, the other when upright.

**Useful For:** Diagnosis of orthostatic proteinuria As a second-order test for additional characterization of proteinuria of less than 3 grams/24 hours, particularly in children or adolescents

**Interpretation:** A supine 8-hour urine protein excretion of less than 68 mg/8 hours together with either 1) an elevated upright (16-hour) excretion of greater than 197 mg/16 hours, or 2) a 24-hour urine protein excretion of greater than 228 mg/24 hours is considered consistent with orthostatic proteinuria.

**Reference Values:**

Nighttime (supine) collection: <68 mg/8 hours

Daytime collection: <197 mg/16 hours

**Osmolality, Feces**

**Clinical Information:** The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors:
- Normal daily dietary intake of electrolytes
- Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure
- Electrolyte transport into fecal water due to exogenous substances and rare toxins (e.g., cholera toxin)

Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Differentiating osmotic from non-osmotic causes of diarrhea is the goal of liquid stool testing. (1,2) The primary way this is accomplished is through the measurement of sodium and chloride and calculation of the osmotic gap, which uses an assumed normal osmolality of 290 mOsm/kg rather than direct measurement of the osmolality. Measurement of osmolality can be useful in the evaluation of chronic diarrhea to help identify whether a specimen has been diluted with hypotonic fluid to simulate diarrhea. (1,3)

**Useful For:** Measurement of osmolality for the workup of cases of chronic diarrhea

**Diagnosis of factitious diarrhea** (where patient adds fluid to stool to simulate diarrhea)

**Interpretation:** Stool osmolality below 220 mOsm/kg indicates dilution with a hypotonic fluid. (1)

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

**Osmolality, Random, Urine**

**Clinical Information:** Osmolality is an index of the solute concentration. Urine osmolality is a measure of the concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts in urine. Urinary osmolality corresponds to urine specific gravity in nondisease states. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine either routinely or under artificial conditions. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality and if urine electrolyte studies are performed. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality.

**Useful For:** Assessing the concentrating and diluting ability of the kidney

**Interpretation:** With normal fluid intake and normal diet, a patient will produce urine of about 500 to 850 mosmol/kg water. Above age of 20 years, there is an age dependent decline in the upper reference range of approximately 5 mOsm/kg/year. The normal kidney can concentrate urine to 800 to 1400 mosmol/kg and with excess fluid intake, a minimal osmolality of 40 to 80 mosmol/kg can be reached. With dehydration, the urine osmolality should be 3 to 4 times the plasma osmolality.

**Reference Values:**
0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

Osmolality, Serum

Clinical Information: Osmolality is a measure of the number of dissolved solute particles in solution. It is determined by the number and not by the nature of the particles in solution. Dissolved solutes change the physical properties of solutions, increasing the osmotic pressure and boiling point and decreasing the vapor pressure and freezing point. Serum osmolality increases with dehydration and decreases with overhydration. The patient receiving intravenous fluids should have a normal osmolality. If the osmolality rises, the fluids contain relatively more electrolytes than water. If the osmolality falls, relatively more water than electrolytes is being administered. Normally, the ratio of serum sodium, in mEq/L, to serum osmolality, in mOsm/kg, is between 0.43 and 0.5. The ratio may be distorted in drug intoxication. Generally, the same conditions that decrease or increase the serum sodium concentration affect the osmolality. A comparison of measured and calculated serum osmolality produces a delta-osmolality. If this is above 40 mOsm/kg H2O in a critically ill patient, the prognosis is poor. An easy formula to calculate osmolality is: Osmolality (mOsm/kg H2O)=2 Na+ Glucose + BUN 20 3

Useful For: Evaluating acutely ill or comatose patients

Interpretation: An increased gap between measured and calculated osmolality may indicate ingestion of poison, ethylene glycol, methanol, or isopropanol.

Reference Values:
275-295 mOsm/kg


Osmolality, Urine

Clinical Information: Osmolality is an index of the solute concentration. Urine osmolality is a measure of the concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts in urine. Urinary osmolality corresponds to urine specific gravity in nondisease states. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine either routinely or under artificial conditions. More information concerning the state of renal water handling, or abnormalities of urine dilution or concentration, can be obtained if urinary osmolality is compared to serum osmolality, and urine electrolyte studies are performed. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality.

Useful For: Assessing the concentrating and diluting ability of the kidney as part of the urinalysis panel

Interpretation: With normal fluid intake and normal diet, a patient will produce urine of about 500 to 850 mOsmol/kg water. Above age of 20 years, there is an age dependent decline in the upper reference range of approximately 5 mOsmol/kg/year. The normal kidney can concentrate urine to 800 to 1,400 mOsmol/kg and with excess fluid intake, a minimal osmolality of 40 to 80 mOsmol/kg can be reached. With dehydration, the urine osmolality should be 3 to 4 times the plasma osmolality.

Reference Values:
Only orderable as a reflex. For more information see: UAR/ Urinalysis with Microscopic.
Osmotic Fragility, Erythrocytes

Clinical Information: Spherocytes are osmotically fragile cells that rupture more easily in a hypotonic solution than do normal RBCs. Because they have a low surface area:volume ratio, they lyse at a higher osmolarity than do normal discocyte (RBCs). Cells that have a larger surface area:volume ratio, such as target cells or hypochromic cells are more resistant to lysing. After incubation, an increase in hemolysis is seen in spherocytes. Hereditary spherocytosis typically has greater number of spherocytes than other causes of spherocytosis. Therefore, the degree of lysis is usually more pronounced, but this is not always the case. Some rare disorders can also cause marked fragility and hereditary spherocytosis cases can display moderate fragility.

Useful For: Evaluation of suspected hereditary spherocytosis associated hemolytic anemia Confirming or detecting mild spherocytosis

Interpretation: An interpretive report will be provided.

Reference Values:
> or =12 months:
- 0.50 g/dL NaCl (unincubated): 3-53% hemolysis
- 0.60 g/dL NaCl (incubated): 14-74% hemolysis
- 0.65 g/dL NaCl (incubated): 4-40% hemolysis
- 0.75 g/dL NaCl (incubated): 1-11% hemolysis

Reference values have not been established for patients who are <12 months of age.


Osmotic Gap, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium.(1) Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars and can be characterized by the following: -Stool volume typically decreased by fasting -Fecal fluid usually has an elevated osmotic gap -Osmotic agents such as magnesium, sorbitol, or polyethylene glycol may be the cause through the intentional or inadvertent use of laxatives -Carbohydrate malabsorption due most commonly to lactose intolerance -Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6) Non-osmotic causes of diarrhea include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia.(1) Secretary diarrhea is classified as non-osmotic and is caused by disruption of epithelial electrolyte transport when secretary agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin are present. The fecal fluid usually has elevated electrolytes (primarily sodium and...
chloride) and a low osmotic gap (<50 mOsm/kg). Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms >4 weeks).

**Useful For:** Workup of cases of chronic diarrhea Differentiating osmotic from non-osmotic causes of chronic diarrhea.

**Interpretation:** Osmotic Gap: -Osmotic gap is calculated as 290 mOsm/kg-(2[Na]+2[K]). Typically, stool osmolality is similar to serum since the gastrointestinal (GI) tract does not secrete water.(1) -An osmotic gap above 50 mOsm/kg is suggestive of an osmotic component contributing to the symptoms of diarrhea.(1-3) -Magnesium-induced diarrhea should be considered if the osmotic gap is above 75 mOsm/kg and is likely if the magnesium concentration is over 110 mg/dL.(1) -An osmotic gap of 50 mOsm/kg or less is suggestive of secretory causes of diarrhea.(1-3) -A highly negative osmotic gap or a fecal sodium concentration greater than plasma or serum sodium concentrations suggests the possibility of either sodium phosphate or sodium sulfate ingestion by the patient.(4) Sodium: -Sodium is typically found at lower concentrations (mean 30 +/- 5 mmol/L) in patients with osmotic diarrhea caused by magnesium-containing laxatives, while typically at higher concentrations (mean 104 +/- 5 mmol/L) in patients known to be taking secretory laxatives.(1) -High sodium and potassium in the absence of an osmotic gap indicate active electrolyte transport in the GI tract that might be induced by agents such as cholera toxin or hypersecretion of vasointestinal peptide.(1)

**Reference Values:**
An interpretive report will be provided


**Osteocalcin, Serum**

**Clinical Information:** Osteocalcin, the most important noncollagen protein in bone matrix, accounts for approximately 1% of the total protein in human bone. It is a 49-amino acid protein with a molecular weight of approximately 5800 daltons. Osteocalcin contains up to 3 gamma-carboxyglutamic acid residues as a result of posttranslational, vitamin K-dependent enzymatic carboxylation. Its production is dependent upon vitamin K and is stimulated by 1,25 dihydroxy vitamin D. Osteocalcin is produced by osteoblasts and is widely accepted as a marker of bone osteoblastic activity. Osteocalcin, incorporated into the bone matrix, is released into the circulation from the matrix during bone resorption and, hence, is considered a marker of bone turnover rather than a specific marker of bone formation. Osteocalcin levels are increased in metabolic bone diseases with increased bone or osteoid formation including osteoporosis, osteomalacia, rickets, hyperparathyroidism, renal osteodystrophy, thyrotoxicosis, and in individuals with fractures, acromegaly and bone metastasis. By means of osteocalcin measurements, it is possible to monitor therapy with antiresorptive agents (bisphosphonates or hormone replacement therapy [HRT]) in, for example, patients with osteoporosis or hypercalcemia. Decrease in osteocalcin is also observed in some disorders (eg, hypoparathyroidism, hypothyroidism, and growth hormone deficiency). Immunochemical and chromatographic studies have demonstrated considerable heterogeneity for concentrations of circulating osteocalcin in normal individuals and in patients with osteoporosis, chronic renal failure, and Paget disease. Both intact osteocalcin (amino acids 1-49) and the large N-terminal/midregion (N-MID) fragment (amino acids 1-43) are present in blood. Intact osteocalcin is unstable due to protease cleavage between amino acids 43 and 44. The N-MID fragment, resulting from cleavage, is considerably more stable. This assay detects both the stable N-MID fragment and intact osteocalcin.
Useful For: Monitoring and assessing effectiveness of antiresorptive therapy in patients treated for osteopenia, osteoporosis, Paget’s disease, or other disorders in which osteocalcin levels are elevated. As an adjunct in the diagnosis of medical conditions associated with increased bone turnover, including Paget’s disease, cancer accompanied by bone metastases, primary hyperparathyroidism, and renal osteodystrophy. This test is not useful for the diagnosis of osteoporosis.

Interpretation: Elevated levels of osteocalcin indicate increased bone turnover. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy: HRT), a decrease of 20% or less from baseline osteocalcin level (ie, prior to the start of therapy) after 3 to 6 months of therapy suggests effective response to treatment. (2) Patients with diseases such as hyperparathyroidism, which can be cured, should have a return of osteocalcin levels to the reference range within 3 to 6 months after complete cure. (3)

Reference Values:

Males
- <5 years: 19-75 ng/mL
- 5-9 years: 21-108 ng/mL
- 10-15 years: 19-159 ng/mL
- 16-17: 12-114 ng/mL
- > or =18 years: 9-42 ng/mL

Females
- <5 years: 14-126 ng/mL
- 5-9 years: 16-152 ng/mL
- 10-15 years: 15-151 ng/mL
- 16-17 years: 9-70 ng/mL
- > or =18 years: 9-42 ng/mL


Ova and Parasite, Concentrate and Permanent Smear, Microscopy, Feces

Clinical Information: A variety of different parasites may be found in stool specimens, duodenal aspirates, and other intestinal specimens. These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (aka worms). Infection is often asymptomatic, but symptoms range from diarrhea and malnutrition, intestinal obstruction, and rarely, death. The most common intestinal reported parasites in stool specimens are Giardia intestinalis (aka Giardia duodenalis, Giardia lamblia) and Cryptosporidium species. Both parasites may cause watery diarrhea and are endemic in the United States. The best tests for these 2 common parasites are parasite-specific fecal antigen tests (GIAR / Giardia Antigen, Feces and CRYPS / Cryptosporidium Antigen, Feces). Other parasites are less commonly seen in the United States, and the stool parasitic exam is the appropriate test for their detection. See Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for determining which test should be ordered based on the patient's exposure history and risk factors. If evaluating a patient for diarrhea, see Laboratory Testing for Infectious Causes of Diarrhea Algorithm.

Useful For: Detection and identification of parasitic protozoa and the eggs and larvae of parasitic helminths

Interpretation: A positive result indicates the presence of the parasite but does not necessarily indicate...
that it is the cause of any symptoms. Some strains of protozoa are nonpathogenic and some helminths cause little or no illness.

**Reference Values:**
Negative
If positive, organism identified


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**OAPNS**

**Ova and Parasite, Microscopy, Varies**

**Clinical Information:** A variety of different parasites may be found in respiratory specimens, liver cyst aspirates or abscesses, and tissues. These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (aka worms). Infection is often asymptomatic, but possible symptoms include diarrhea and malnutrition, intestinal obstruction, and rarely, death.

**Useful For:** Detection and identification of parasitic protozoa and the eggs and larvae of parasitic helminths

**Interpretation:** A positive result indicates the presence of the parasite but does not necessarily indicate that it is the cause of the patient's symptoms. Some strains of protozoa are nonpathogenic and some helminths cause little or no illness.

**Reference Values:**
Negative
If positive, organism identified


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**OVAL**

**Ovalbumin, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to ovalbumin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class IgE kU/L  Interpretation

FOVAS

Ovarian Antibody Screen with Reflex to Titer, IFA

Reference Values:

Negative
Ovarian antibody screen is at 1:5 dilution

OVMU

Ovomucoid, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ovomucoid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

Ox-Eye Daisy, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ox-eye daisy Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

OXA-48 and VIM, PCR (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**OXVRP 65043**
OXA-48-like (blaOXA-48-like) and VIM (blaVIM) in Gram-Negative Bacilli, Molecular Detection, PCR, Varies

Clinical Information: In the United States, Klebsiella pneumoniae carbapenemase (KPC) is the most common carbapenemase, followed by New Delhi metallo-beta-lactamase (NDM). OXA-48-like and VIM carbapenemases predominate in other parts of the globe, but do occur in the United States. The genes blaOXA-48-like and blaVIM encode OXA-48-like and VIM enzyme production, respectively. PCR is a sensitive, specific, and rapid means of identifying these genes. This test detects the genes encoding OXA-48-like (oxacillin-hydrolyzing beta-lactamase) and VIM (Verona integron-encoded metallo-beta-lactamase) types of beta-lactamases in bacterial isolates.

Useful For: Assessing pure isolates of Gram-negative bacilli for mechanism of carbapenem resistance

Interpretation: This PCR detects and differentiates blaOXA-48-like and blaVIM. A positive blaOXA-48-like (oxacillin-hydrolyzing beta-lactamase) PCR indicates that the isolate carries blaOXA-48-like. A positive VIM (Verona integron-encoded metallo-beta-lactamase) PCR indicates the isolate carries blaVIM. A negative result indicates the absence of detectable DNA.

Reference Values:
Not applicable

Clinical References:

**OVSRP 65042**
OXA-48-like (blaOXA-48-like) and VIM (blaVIM) Surveillance, PCR, Varies

Clinical Information: In the United States, Klebsiella pneumoniae carbapenemase (KPC) is the most common carbapenemase, followed by New Delhi metallo-beta-lactamase (NDM). OXA-48-like and VIM carbapenemases predominate in other parts of the globe, but do occur in the United States. The genes blaOXA-48-like and blaVIM encode OXA-48-like and VIM enzyme production, respectively. PCR is a sensitive, specific, and rapid means of identifying these genes. This test detects the genes encoding OXA-48-like (oxacillin-hydrolyzing beta-lactamase) and VIM (Verona integron-encoded metallo-beta-lactamase) types of beta-lactamases in feces and perirectal/rectal/perianal/anal swabs. It can be used as a tool to find colonized patients. The Centers for Disease Control and Prevention recommends surveillance to detect unrecognized colonized patients who may be a potential source for transmission of carbapenemase-producing Gram-negative bacilli under certain circumstances. Such surveillance may be focused in certain high-risk settings or patient groups (eg, ICUs, long-term care facilities, patients transferred from areas or facilities with a high prevalence of the relevant type of resistance) or may be directed by infection prevention and control to investigate an outbreak.

Useful For: Identifying carriers of Gram-negative bacilli harboring OXA-48-like (oxacillin-hydrolyzing beta-lactamase) or VIM (Verona integron-encoded metallo-beta-lactamase) genes
Interpretation: This PCR assay detects and differentiates blaOXA-48-like and blaVIM in surveillance specimens (perirectal/rectal/perianal/anal swabs or feces). A positive OXA-48-like (oxacillin-hydrolyzing beta-lactamase) and/or VIM (Verona integron-encoded metallo-beta-lactamase) PCR indicates that the patient is colonized by a Gram-negative bacillus (or Gram-negative bacilli) harboring blaOXA-48-like and/or blaVIM, respectively. A negative result indicates the absence of detectable DNA.

Reference Values:
Not applicable

Clinical References:

Oxalate Analysis, Hemodialysate

Clinical Information: Oxalate is a dicarboxylic acid, an end product of glyoxalate and glycerate metabolism that is excreted in the urine where it is a common component of kidney stones (up to 85%). Hyperoxaluria can be either genetic (eg, primary hyperoxaluria) or acquired/secondary (eg, enteric hyperoxaluria), and can lead to nephrocalcinosis and renal failure. Monitoring the adequacy of oxalate removal during hemodialysis can be useful in the management of patients with hyperoxaluria and renal failure, particularly following transplantation.

Useful For: Determining the amount of oxalate removed during a dialysis session Individualizing the dialysis prescription of hyperoxaluric patients

Interpretation: An exponential decrease in oxalate signal is expected through dialysis procedure. Signals below 2 mcM at any point during dialysis suggest that the plasma has been effectively cleared, although there can be rebound after dialysis ceases. Total oxalate removed during a dialysis session can be estimated by multiplying the concentration of oxalate in the dialysate by the oxalate flow rate for each time period that the oxalate is measured.

Reference Values:
Not applicable

Clinical References:

Oxalate, 24 Hour, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans do not have an enzyme capable of degrading oxalate, therefore it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic to renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat
malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C (ascorbic acid). Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

**Useful For:** Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

**Interpretation:** An elevated urine oxalate (>0.46 mmol/24 hours) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation.

**Reference Values:**
- 0.11-0.46 mmol/24 hours
- 9.7-40.5 mg/24 hours

The reference value is for a 24-hour collection. Specimens collected for other than a 24-hour time period are reported in unit of mmol/L for which reference values are not established.

Reference values have not been established for patients who are less than 16 years of age.

**Clinical References:**

**POXA1**

Oxalate, Plasma

**Clinical Information:** Oxalate is an insoluble dicarboxylic acid, which is an end product of liver metabolism of glyoxalate and glycerate. Humans lack an enzyme to degrade oxalate, and thus it must be eliminated by the kidney. Oxalate is a strong anion and tends to precipitate with calcium, especially in the urinary tract. Consequently, about 75% of all kidney stones contain calcium oxalate in some proportion. In renal failure oxalate is retained in the body, and it can precipitate in tissues causing tissue toxicity, a condition called oxalosis. In the absence of disease, up to 90% of the body pool of oxalate is produced by hepatic metabolism and the other 10% is provided by oxalate contained in various foods. However, in the presence of gastrointestinal diseases that cause fat malabsorption, the percentage of oxalate absorbed from food can be much greater. The oxalate content of fruits and vegetables is quite variable, some being quite high and others virtually zero. Oxalate is freely filtered by the glomerulus. A smaller amount is also secreted in the proximal tubule. If the glomerular filtration rate (GFR) is decreased, oxalate begins to be retained in the body. However, in persons without primary hyperoxaluria (PH) or enteric hyperoxaluria (EH), plasma oxalate levels do not exceed the normal range until the GFR decreases below 10-20 mL/min/1.73 m(2). Plasma oxalate concentration is a reflection of the body pool size. When the pool increases, oxalate may precipitate in tissues and cause toxicity. Plasma oxalate pool size can be increased in various situations: Increased production and accumulation results from an abnormality in at least 3 different enzymes: Alanine glyoxalate transferase is necessary for the conversion of glycolate to alanine. A deficiency or intracellular mistargeting of this hepatic enzyme results in increased oxalate production (primary hyperoxaluria type 1). Glycolate reductase/hydroxypropyruvate reductase deficiency in the liver and elsewhere in the body results in increased glyceric acid formation, which leads to increased oxalate production (primary hyperoxaluria type 2). A third type of PH was recently shown to be due to variants of HOXA1 that encodes the enzyme 4-hydroxy-2-oxalosugar aldolase that is found in hepatic mitochondria (primary hyperoxaluria type 3). Increased oxalate load can be caused by increased absorption from the intestines after consuming large amounts of oxalate-rich foods such as rhubarb, spinach, or nuts. Certain abnormalities of the gastrointestinal tract can cause fat malabsorption including short bowel syndromes, inflammatory bowel disease, gastric bypass for obesity, and pancreatic insufficiency. All of these gastrointestinal abnormalities result in increased oxalate absorption from the
intestinal tract. This condition referred to as EH is due to saponification of calcium by fatty acids in the colon, which in turn frees up oxalate anions for absorption. Decreased urinary oxalate excretion in chronic kidney disease (CKD) also causes oxalate retention in the body. Management of patients with PH and renal failure is difficult. Intensive dialyses are undertaken in an attempt to keep plasma levels below the level at which supersaturation and crystallization can occur in body tissues such as heart and bones (called oxalosis). PH is typically diagnosed by measuring oxalate levels in urine. However, as kidney function decreases, the renal excretion of oxalate also decreases. In such situations, plasma oxalate levels are often be informative. Although plasma oxalate increases in CKD patients without PH, values are much higher in those CKD patients who do have PH or EH. Plasma oxalate is often used to monitor these patients during critical periods in and around kidney transplantation, dialysis, or liver transplantation. Oxalate concentration in dialysate fluid is a reflection of the oxalate removed during dialysis.

**Useful For:**
- Assessing the body pool size of oxalate in patients with enzyme deficiencies, such as primary hyperoxaluria (PH), or patients with enteric hyperoxaluria (EH)
- Aiding in the diagnosis of PH in a patient with chronic kidney disease (CKD) of indeterminate cause when urinary oxalate is not available
- Monitoring patients with renal failure and primary or enteric hyperoxaluria in order to be sure they are receiving enough dialysis
- Aiding in maintaining plasma oxalate levels below supersaturation (25-30 mcmol/L)

**Interpretation:**

In patients with normal renal function, the presence of increased plasma oxalate concentration is good evidence for overproduction of oxalate (primary hyperoxaluria: PH). In the presence of renal insufficiency, plasma oxalate levels can be markedly elevated in patients with PH or enteric hyperoxaluria (EH). Increased levels of plasma oxalate can be found in dialysis patients without EH or PH, but the degree of elevation is less. In patients with possible primary hyperoxaluria and renal insufficiency, the diagnosis often can be presumptively made by knowing the plasma level of oxalate. However, ancillary tests, such as the demonstration of oxalate crystals in tissues (other than the kidney) or increased glycolate in dialysate (for patients on dialysis) are frequently necessary to make an accurate diagnosis.

**Reference Values:**

≤2.0 mcmol/L

Reference values have not been established for patients under 18 years old or greater than 87 years of age.

**Clinical References:**
creatinine ratio varies widely in young children from <0.35 mmol/mL at birth, to <0.15 mmol/mL at 1 year, to <0.10 mmol/mL at 10 years, and <0.05 mmol/mL at 20 years of age (see table below).(1) Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048

Reference Values:
No established reference values


Oxalate, Random, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

Useful For: Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

Interpretation: An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from <0.35 mmol/mL at birth, to <0.15 mmol/mL at 1 year, to <0.10 mmol/mL at 10 years, and <0.05 mmol/mL at 20 years of age (see table below).(1) Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048

Reference Values:
Only orderable as part of a profile. For more information see ROXUR / Oxalate, Random, Urine.

No established reference values

Oxalate/Creatinine Ratio, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

Useful For: Calculating the oxalate concentration per creatinine

Interpretation: An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients with high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from <0.35 mmol/mL at birth to <0.15 mmol/mL at 1 year to <0.10 mmol/mL at 10 years and <0.05 mmol/mL at 20 years of age (see table below). (1)

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<th>Age (year)</th>
<th>95th Percentile</th>
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<td>&lt;0.056</td>
</tr>
<tr>
<td>7-17</td>
<td>&lt;0.048</td>
</tr>
</tbody>
</table>

Reference Values: Only orderable as part of a profile. For more information see ROXUR / Oxalate, Random, Urine.

No established reference values.


Oxazepam (Serax), Serum

Reference Values: Reference Range: 200 - 500 ng/mL

Oxcarbazepine Metabolite, Serum

Clinical Information: Oxcarbazepine (OCBZ) is approved as monotherapy and adjunctive therapy for partial seizures with and without secondary generalized seizures in adults and as adjunctive therapy for partial seizures in children. In humans, OCBZ is a prodrug that is almost immediately and completely metabolized to 10-hydroxy-10,11-dihydrocarbamazepine, known as monohydroxycarbamazepine (MHC), an active metabolite that is responsible for OCBZ's therapeutic effect. The elimination half-life is 1 to 2.5 hours for OCBZ and 8 to 10 hours for MHC. The therapeutic range (10-35 mcg/mL) is based on concentrations of the metabolite, not the parent drug; this assay measures the metabolite only. In clinical practice, the OCBZ dosage should be individually adjusted for each patient to achieve the desired therapeutic response. Toxicity associated with OCBZ includes hyponatremia, dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision,
abdominal pain, tremor, dyspepsia, and abnormal gait. These toxicities may be observed when blood concentrations are in the therapeutic range.

**Useful For:** Monitoring serum concentration during oxcarbazepine therapy Assessing compliance Assessing potential toxicity

**Interpretation:** Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Most individuals display optimal response to oxcarbazepine therapy when serum levels of the metabolite (measured in this assay) are between 10 and 35 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range. Thus, interpretation should include clinical evaluation.

**Reference Values:**
Oxcarbazepine metabolite: 10-35 mcg/mL


### Oxycodone - Free (Unconjugated), Serum

**Reference Values:**
Reporting Limit determined each analysis.

**Oxycodone - Free (ng/mL)**

Adult therapeutic range: 13 - 120 ng/mL

### Oxycodone Screen, Chain of Custody, Random, Urine

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone). Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detection of oxycodone and oxymorphone in urine following chain-of-custody procedures
This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.
**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, OXYCU / Oxycodone with Metabolite Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing.

**Reference Values:**
Negative
Screening cutoff concentration:
Oxycodone: 100 ng/mL

**Clinical References:**
3. Cone EJ: Oxycodone Involvement in Drug Abuse Deaths: A DAWN-Based Classification Scheme applied to an Oxycodone Postmortem Database Containing over 1000 Cases. J Anal Toxicol 2003;27:57-67

**OXYSU 62623**

**Oxycodone Screen, Random, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone). Oxycodone is metabolized to noroxycodone, oxymorphone and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone.

**Useful For:** Detection of oxycodone and oxymorphone in urine

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, OXYCU / Oxycodone with Metabolite Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html.

**Reference Values:**
Negative
Screening cutoff concentration:
Oxycodone: 100 ng/mL

**Clinical References:**
3. Cone EJ: Oxycodone Involvement in Drug Abuse Deaths: A DAWN-Based Classification Scheme applied to an Oxycodone Postmortem Database Containing over 1000 Cases. J Anal Toxicol 2003;27:57-67
glucuronides and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and quantification of oxycodone, oxymorphone, noroxycodone, and noroxymorphone in urine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations:
- Oxycodone Immunoassay screen: 100 ng/mL
- Oxycodone-by LC-MS/MS: 25 ng/mL
- Noroxycodone-by LC-MS/MS: 25 ng/mL
- Oxymorphone-by LC-MS/MS: 25 ng/mL
- Noroxymorphone-by LC-MS/MS: 25 ng/mL

**Clinical References:**

**OxyCU**

**Clinical Information:** Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of oxycodone, oxymorphone, noroxycodone, and noroxymorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations:
- Oxycodone-by LC-MS/MS: 25 ng/mL
- Noroxycodone-by LC-MS/MS: 25 ng/mL
- Oxymorphone-by LC-MS/MS: 25 ng/mL
- Noroxymorphone-by LC-MS/MS: 25 ng/mL
**Clinical References:**

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**OXY MU**

**Oxymorphone Confirmation, Random, Urine**

**Clinical Information:** Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of oxymorphone and noroxymorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations:
- Oxymorphone-by LC-MS/MS: 25 ng/mL
- Noroxymorphone-by LC-MS/MS: 25 ng/mL

**Clinical References:**

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**OXY WB**

**Oxysterols, Blood**

**Clinical Information:** Niemann-Pick disease types A, B, and C (NPA, NPB, and NPC, respectively) are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. NPA and NPB are caused by a deficiency of sphingomyelinase that results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. NPA disease is more severe than NPB and is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by age 3 years. NPB disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Large lipid-laden foam cells are characteristic of the disease. Approximately 50% of cases have cherry-red spots in the macula. Sphingomyelinase is encoded by the SMPD1 gene. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are pan-ethnic. Individuals with NPA and NPB typically have elevations of the lyso-sphingomyelin (LSM) and lyso-sphingomyelin 509 (LSM 509) combined with potential elevations in cholestan-3-beta, 5-alpha, 6-beta-triol (COT) and 7-ketocholesterol (7-KC). Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis, Varies). NPC is caused by a defect in cellular cholesterol trafficking that results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. (1) NPC is considered a lipid storage disorder with variable age of onset (range: perinatal period to adulthood), and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without
hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by variants in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol cholestane-3-beta, 5-alpha, 6-beta-triol (COT); lyso-sphingomyelin 509 (LSM 509) and 7-ketocholesterol (7-KC) may also be elevated. The diagnosis of NPC can be confirmed by demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts (NIEM / Niemann-Pick Type C Detection, Fibroblasts). For molecular confirmation, genetic testing for NPC disease can be performed (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis, Varies).

**Useful For:** Investigation of possible diagnoses of Niemann-Pick disease types A, B, or C in blood spot specimens Monitoring of individuals with Niemann-Pick type C disease This test is not suitable for the identification of carriers.

**Interpretation:** An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol (COT) is highly suggestive of Niemann-Pick disease type C (NPC) disease. An elevation of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick disease type A or B (NPA or NPB) disease. An elevation of lyso-sphingomyelin 509 (LSM 509) is suggestive of NPA, NPB, or NPC disease.

**Reference Values:**

**CHOLESTANE-3-BETA, 5-ALPHA, 6-BETA-TRIOL**

Cutoff: < or =0.800 nmol/mL

**LYSO-SPHINGOMYELIN**

Cutoff: < or =0.100 nmol/mL

**Clinical References:**

**OXYBS**

Oxysterols, Blood Spot

**Clinical Information:** Niemann-Pick disease types A, B, and C (NPA, NPB, and NPC, respectively) are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids
within cells. NPA and NPB are caused by a deficiency of sphingomyelinase that results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. NPA disease is more severe than NPB and is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by age 3 years. NPB disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula.

Sphingomyelinase is encoded by the SMPD1 gene. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are panethnic. Individuals with NPA and NPB typically have elevations of lyso-sphingomyelin (LSM) and lyso-sphingomyelin 509 (LSM 509) combined with potential elevations in cholestane-3 beta, 5 alpha, 6 beta-triol (COT) or 7-ketocholesterol (7-KC). Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis, Varies). NPC is caused by a defect in cellular cholesterol trafficking that results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes.(1) NPC is considered a lipid storage disorder with variable age of onset (range: perinatal period to adulthood), and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. (2) Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by variants in either the NPC1 or NPC2 genes. Most individuals with NPC exhibit elevated levels of oxysterol cholestane-3 beta, 5 alpha, 6 beta-triol (COT) in dried blood spots, however, testing in plasma (OXNP / Oxysterols, Plasma) is more sensitive, particularly in patients with an atypical presentation. Elevations may also be seen in lyso-sphingomyelin 509 (LSM 509) and 7-ketocholesterol (7-KC). The diagnosis of NPC can be confirmed by demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts (NIEM / Niemann-Pick Type C Detection, Fibroblasts) or by molecular genetic analysis of the NPC1 and NPC2 genes (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis, Varies).

Useful For: Investigation of possible diagnosis of Niemann-Pick disease types A, B, or C in blood spot specimens Monitoring of individuals with Niemann-Pick disease type C This test is not suitable for the identification of carriers.

Interpretation: An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol (COT) is highly suggestive of Niemann-Pick disease type C (NPC) disease. An elevation of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick disease type A or B (NPA or NPB) disease. An elevation of lyso-sphingomyelin 509 (LSM 509) is suggestive of NPA, NPB or NPC disease.

Reference Values:

CHOLESTANE-3-BETA,5-ALPHA,6-BETA-TRIOL
Cutoff: < or =0.800 nmol/mL

LYSO-SPHINGOMYE LIN
Cutoff: < or =0.100 nmol/mL

Clinical Information: Niemann-Pick disease types A, B, and C (NPA, NPB, and NPC, respectively) are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. NPA and NPB are caused by a deficiency of sphingomyelinase that results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. NPA disease is more severe than NPB and is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by age 3 years. NPB disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula.

Sphingomyelinase is encoded by the SMPD1 gene. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are panethnic. Individuals with NPA and NPB typically have elevations of lyso-sphingomyelin (LSM) and lyso-sphingomyelin 509 (LSM 509) combined with potential elevations in cholestane-3 beta, 5 alpha, 6 beta-triol or 7-ketocholesterol (7-KC). Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis, Varies). NPC is caused by a defect in cellular cholesterol trafficking that results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. NPC is considered a lipid storage disorder with variable age of onset (range: perinatal period to adulthood), and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by variants in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol cholestane-3 beta, 5 alpha, 6 beta-triol and 7-ketocholesterol (7-KC); lyso-sphingomyelin 509 (LSM 509) and 7-ketocholesterol (7-KC) may also be elevated. The diagnosis of NPC can be confirmed by demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts (NIEM / Niemann-Pick Type C Detection, Fibroblasts). For molecular confirmation, genetic testing for NPC disease can be performed (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis, Varies).

Useful For: Investigation of possible diagnoses of Niemann-Pick disease types A, B, or C in plasma specimens Monitoring of individuals with Niemann-Pick type C disease This test is not useful for the identification of carriers.

Interpretation: An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol (COT) is highly suggestive of Niemann-Pick disease type C (NPC). An elevation of lyso-sphingomyelin (LSM) is highly suggestive of
Niemann-Pick type A or B (NPA or NPB) disease. An elevation of lyso-sphingomyelin 509 (LSM 509) is suggestive of NPA, NPB, or NPC disease.

Reference Values:
CHOLESTANE-3-BETA, 5-ALPHA, 6-BETA-TRIOL
Cutoff: < or =0.070 nmol/mL

7-KETOCHESTEROL
Cutoff: < or =0.100 nmol/mL

LYSO SPHINGOMYELIN
Cutoff: < or =0.100 nmol/mL


Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to oyster Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**p16 (INK4a/CDKN2A) Immunostain, Technical Component Only**

**Clinical Information:** p16 (INK4a/CDKN2A) is a cell cycle regulatory protein that is overexpressed in cervical dysplasia related to human papilloma virus (HPV) infection. Nuclear and cytoplasmic staining is seen in dysplastic squamous cervical epithelial cells infected with HPV, but not in normal cells. A subset of pancreatic islet cells and dendritic cells show expression of p16, and can serve as positive control.

**Useful For:** Aids in the identification of human papilloma virus infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Doxtader EE, Katzenstein AL: The relationship between p16 expression and high-risk human papillomavirus infection in squamous cell carcinomas from sites other than uterine cervix: a study of 137 cases. Human Pathol 2012;43:327-332
**p40 + Napsin A Immunostain, Technical Component Only**

**Clinical Information:** p40 is an antibody (detected by the chromogen 3,3'-diaminobenzidine (DAB)) that recognizes the deltaNp63 isoform of p63. This isoform may exert an oncogenic effect and is selectively expressed in squamous cell carcinoma. Napsin A is an aspartic proteinase involved in the proteolytic processing of surfactant precursors in the normal alveolar epithelium. In normal tissues, napsin A is expressed in the cytoplasm of alveolar macrophages, type II pneumocytes, pancreatic ducts and acini, and in renal tubules (detected by the chromogen fast red). Napsin A has clinical utility for the identification of primary lung adenocarcinomas. Napsin A is also positive in a subset of thyroid and renal cell carcinomas (especially papillary types).

**Useful For:** p40 aids in the classification of carcinomas and lymphomas Napsin A aids in the identification of primary lung adenocarcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**p40 Immunostain, Technical Component Only**

**Clinical Information:** p40 is an antibody that recognizes the deltaNp63 isoform of p63. This isoform may exert an oncogenic effect and is selectively expressed in squamous cell carcinoma.

**Useful For:** Diagnosis and classification of carcinomas and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**P53**

**p53 Immunostain, Technical Component Only**

**Clinical Information:** p53 is a tumor-suppressor protein. Genetic events (variant and deletion) that affect both p53 alleles can lead to loss of cell cycle control in the setting of DNA damage, resulting in genetic instability and neoplastic transformation. Altered p53 also has a prolonged half-life compared to wild-type p53 and, thus, accumulates in the nucleus and can be detected by immunohistochemistry. Abnormalities of the p53 gene are one of the most common genetic changes associated with cancer and can be found in a wide variety of tumor types, where they are generally associated with a worse prognosis. The p53 protein can be readily detected in a subset of cancers of the colon, stomach, bladder, breast, lung, and testes and in melanoma and lymphoma.

**Useful For:** Aiding in the identification of neoplastic cells

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**P57I**

**p57 (KIP2/CDKN1C) Immunostain, Technical Component Only**

**Clinical Information:** p57 (KIP2/CDKN1C) is a cell cycle regulatory protein that acts as a tumor-suppressor gene by inhibiting the activity of cyclin dependent kinases. p57 is expressed in the cytotrophoblasts, intermediate trophoblasts, and villous stromal cells in normal placenta. Loss of p57 expression is associated with complete hydatidiform moles, and can help distinguish them from partial hydatidiform moles and hydropic abortions.

**Useful For:** Aids in the identification of cytotrophoblasts, intermediate trophoblasts, and villous stromal cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full...
All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**P62 Immunostain, Technical Component Only**

**Clinical Information:** Argyrophilic grain disease (AGD) is a common, late-onset dementia characterized by the presence of argyrophilic grains and coiled bodies. AGD is a frequent pathologic finding in patients who have been diagnosed with amnestic-type mild cognitive impairment. Immunohistochemical detection of ubiquitin-binding protein p62 is a sensitive and reproducible method to identify grain pathology in AGD.

**Useful For:** Aids in diagnosing argyrophilic grain disease

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**P63 Immunostain, Technical Component Only**

**Clinical Information:** The p63 protein is a member of the p53 family of tumor-suppressor proteins. The predominant localization of p63 protein is in the basal layer of stratified squamous and transitional epithelia. p63 is negative in malignant tumors of the prostate. Striated muscle staining may be observed with p63.

**Useful For:** Aiding in identifying squamous, urothelial, or myoepithelial differentiation in tumors

**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

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**Pacific Squid, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to pacific squid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Pain Clinic Drug Screen, Chain of Custody, Urine

Clinical Information: This panel was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID) the following drugs: -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This panel uses the screening technique that involves immunoassay testing for drugs by class. All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS, and quantitated, before a positive result is reported. The panel includes PDSUX / Drug Screen, Prescription/OTC, Chain of Custody, Urine, which looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The test is not designed to screen for intermittent use of illicit drugs. Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol Detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent This test is intended to be used in a setting where the identification of the drug is required. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html.

Reference Values:
Negative

Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Pain Clinic Drug Screen, Urine**

**Clinical Information:** This panel was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID) the following drugs: -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This panel uses the screening technique which involves immunoassay testing for drugs by class. All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS, and quantitated, before a positive result is reported. The panel includes PDSU / Drug Screen, Prescription/OTC, Urine, which looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The test is not designed to screen for intermittent use of illicit drugs.

**Useful For:** Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol Detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent This test is intended to be used in a setting where the identification of the drug is required.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at https://www.mayocliniclabs.com/test-info/drug-book/index.html.

**Reference Values:**
Negative

Screening cutoff concentrations:
- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 100 ng/mL
- Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
- Ethanol: 10 mg/dL
- Methadone metabolite: 300 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


**Pain Clinic Survey 10, Chain of Custody, Random, Urine**

**Reference Values:**
Only orderable as part of a profile. For more information see PANOX / Pain Clinic Survey 10, Chain of Custody, Urine.
Pain Clinic Survey 10, Chain of Custody, Random, Urine

Clinical Information: This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) the following: -Barbiturates -Benzodiazepines -Cocaine -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This test uses the simple screening technique which involves immunologic testing for drugs by class. Oxycodone is not detected well with the opiate screening assay; therefore, OPATX / Opiate Confirmation, Chain of Custody, Urine is included to detect this drug. All positive screening results are confirmed by GC-MS or LC-MS/MS, and quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This chain-of-custody test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Interpretation: A positive result derived by this testing indicates that the patient has used 1 of the drugs detected by these techniques in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing.

Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


Paliperidone, Serum

Interpretation: Paliperidone (9-hydroxyrisperidone) is the active ingredient in Invega extended-release tablets. Paliperidone is also the major active metabolite of Risperidone. Steady-state concentrations are typically attained within 4 to 5 days of dosing. Following daily administration of 12 mg extended release formulation, paliperidone steady state plasma concentrations ranged from 30 to 40 ng/mL.

Reference Values:
Reporting limit determined each analysis.

Units: ng/mL
**Pancreatin, Plasma**

**Clinical Information:** Pancreatin is a 49 amino acid peptide produced by degradation of Chromo-granin A. It inhibits Chromogranin A and Parathyroid Hormone release. Pancreatin also inhibits release of Somatostatin upon glucose stimulation. It may also control carbohydrate metabolism and hyperglycemia. Although there are no compounds with significant structural homology with Pancreatin, there are minor similarities to Gastrin and Anti-Diuretic Hormone. Pancreatin reduces the early phase of Glucose induced Insulin release. Suppression of Insulin release upon Glucose stimulation is a characteristic feature of Type II Diabetes. Pancreatin could play an important therapeutic role in the treatment of diabetes. Pancreatin also inhibits release of Somatostatin. It may also control carbohydrate metabolism and hyperglycemia.

**Reference Values:**

10-135 pg/mL

**Clinical References:**

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**Pancreatic Elastase, Feces**

**Clinical Information:** Pancreatic elastase (PE) is a proteolytic enzyme produced in the pancreatic acinar cells. It is released as a zymogen, which is then converted to an active enzyme in the duodenum by trypsin. PE has an important role in digestion, and proteolytically degrades proteins preferentially at alanine residues. Exocrine pancreatic insufficiency (EPI) is described as a reduction in pancreatic enzyme activity below the normal digestive threshold level. Clinical symptoms of EPI include steatorrhea, bloating, abdominal discomfort, and weight loss. EPI is most commonly caused by chronic pancreatitis but can also be associated with pancreatic cancer, pancreatic surgery, necrotizing acute pancreatitis, cystic fibrosis, inflammatory bowel disease (both Crohnâ€™s disease and ulcerative colitis), diabetes (types I and II), gastric surgery, short bowel syndrome, and Zollinger-Ellison syndrome. If left untreated, patients with EPI can experience weight loss and significant nutrient deficiencies. Treatment for EPI centers on administration of pancreatic enzyme replacement therapy. Stool testing is a critical component for the diagnosis of EPI. The 72-hour fecal fat test is useful for evaluating for the presence of steatorrhea. However, this testing is cumbersome for the patient and not easily tolerated due to the requirement of consuming 100 g fat/day. An alternate to the 72-hour fecal fat test is the measurement of PE in stool. The amount of PE in stool is representative of pancreatic enzyme production; patients with EPI may have reduced concentrations of PE in feces.

**Useful For:** Diagnosis of exocrine pancreatic insufficiency in case of unexplained diarrhea, constipation, steatorrhea, flatulence, weight loss, upper abdominal pain, and food intolerances. Monitoring of exocrine pancreatic function in cystic fibrosis, diabetes mellitus, or chronic pancreatitis.
Interpretation: Pancreatic elastase concentrations above 200 mcg/g are normal and are not indicative of exocrine pancreatic insufficiency. Pancreatic elastase concentrations from 100-200 mcg/g are suggestive for moderate exocrine pancreatic insufficiency. Pancreatic elastase concentrations below 100 mcg/g are consistent with exocrine pancreatic insufficiency.

Reference Values:
- <100 mcg/g (Severe Pancreatic Insufficiency)
- 100-200 mcg/g (Moderate Pancreatic Insufficiency)
- >200 mcg/g (Normal)

Reference values apply to all ages.


Pancreatic Polypeptide, Plasma

Clinical Information: Pancreatic polypeptide (PP) is secreted by the pancreas in response to hypoglycemia, ingestion of food, or "sham" feeding (food is chewed, but not swallowed) secondary to vagal nerve stimulation. Secretion is blocked by vagotomy or atropine. The exact physiologic role of PP is undetermined, although the hormone is thought to be involved in exocrine pancreatic secretion and gallbladder emptying. Markedly elevated levels are often associated with endocrine tumors of the pancreas (eg, insulinoma, glucagonoma, PPoma: pancreatic polypeptide-secreting tumor of the pancreas) Patients with diabetes may also have elevated PP levels. A lack of response to sham feeding may indicate vagal nerve damage (eg, surgery-related nerve damage, autonomic nerve disorders). Extensive pancreatic destruction (eg, chronic pancreatitis, pancreatic cancer) may also result in low basal PP levels and a lack of response to sham feeding.

Useful For: Detection of pancreatic endocrine tumors Assessment of vagal nerve function after meal or sham feeding

Interpretation: High levels may be seen in pancreatic endocrine tumors, diabetes, and a nonfasting state. Markedly elevated levels may be seen in some pancreatic exocrine tumors. A normal response to a sham feeding consists of a rapid pancreatic polypeptide (PP) rise over baseline followed by a return to baseline. With vagal damage, no increase over baseline is seen.

Reference Values:
- 0-19 years: not established
- 20-29 years: <228 pg/mL
- 30-39 years: <249 pg/mL
- 40-49 years: <270 pg/mL
- 50-59 years: <291 pg/mL
- 60-69 years: <312 pg/mL
- 70-79 years: <332 pg/mL
- > or =80 years: not established

Papaya, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to papaya
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens:
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
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<th>IgE kU/L</th>
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<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
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<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Paprika, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to paprika Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<td>2</td>
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<td>50.0-99.9</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
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**Parafibromin, Immunostain, Technical Component Only**

**Clinical Information:** Parafibromin is a protein encoded by the HRPT2 oncosuppressor gene, and the expression is reported to be decreased or absent in parathyroid carcinomas. Parafibromin is expressed in the nucleus of benign parathyroids, parathyroid adenomas, and other normal tissues, but shows loss of expression in parathyroid carcinomas, making it a good diagnostic tool to identify parathyroid carcinomas and distinguish them from parathyroid adenomas.

**Useful For:**

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Paraneoplastic Pemphigus Antibody (IgG), Serum**

**Clinical Information:** Paraneoplastic pemphigus (PNP; also paraneoplastic autoimmune multiorgan syndrome: PAMS, to denote the systemic nature of the syndrome) is an autoimmune mucocutaneous blistering disease affecting adults or rarely children that generally heralds the presence of an underlying malignancy. PNP/PAMS can be defined and identified by a combination of the following features: 1) painful stomatitis and a polymorphous cutaneous eruption with lesions that may be blistering, lichenoid, erythema multiforme-like or morbilliform; 2) variable histopathologic findings, including acantholysis, lichenoid, or interface change; 3) variable direct immunofluorescence findings from a perilesional biopsy, often demonstrating deposition of IgG and complement in the epidermal intercellular spaces, granular/linear complement deposition along the epidermal basement membrane zone, and/or a lichenoid tissue reaction; 4) indirect immunofluorescence evidence of cell surface deposition on monkey esophagus and/or rat bladder epithelium; 5) ELISA evidence of serum autoantibodies against desmogleins 1 or 3, and possibly against bullous pemphigoid (BP) 180 and 230 antigens. The incidence of the disease is unknown but it is less common than pemphigus vulgaris (PV) or foliaceus (PF). Clinical features of the disease can mimic those seen in a drug reaction, erythema multiforme, Stevens-Johnson syndrome, pemphigus, lichen planus, or toxic epidermal necrolysis. PNP/PAMS is associated in the majority of cases with non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, or Castleman disease. A serious complication includes bronchiolitis obliterans, which may lead to respiratory failure.

**Useful For:** Diagnosis of paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome (PNP/PAMS) in the setting of erosive or lichenoid mucocutaneous disease

**Interpretation:** In the appropriate clinical setting, a positive result can support a diagnosis of paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome (PNP/PAMS). However, correlation with clinical features, histopathologic findings, results of serum studies (such as indirect immunofluorescence on monkey esophagus substrate and ELISA for Dsg1/3) is required for a final diagnosis. As the test is not entirely sensitive, a negative test result does not exclude the possibility of PNP/PAMS.

**Reference Values:**
Report as positive or negative.
Negative in normal individuals.

**Clinical References:**

---

**Paraneoplastic Vision Loss Evaluation, Serum**

**Clinical Information:** There are 2 recognized forms of paraneoplastic vision loss: paraneoplastic autoimmune optic neuropathy with retinopathy accompanying collapsin response-mediator protein-5 (CRMP-5)-IgG, and cancer associated retinopathy (CAR) accompanying recoverin antibody. Both occur in the setting of occult small cell carcinoma of the lung or other body region. Patients with CRMP-5-IgG associated optic neuropathy typically present with painless bilateral visual loss over weeks to months. At onset, there is typically bilateral optic disc edema without evidence of enhancement of the optic nerve on magnetic resonance imaging or elevated opening pressure on lumbar puncture. Visual acuity can range from 20/20 to hand motion. Patients typically have co-existing vitritis or retinitis. In addition, patients can have diplopia, typically from cerebellar involvement. The majority of patients with CRMP-5 associated optic neuropathy will have other neurologic deficits from CRMP-5 autoimmunity, such as asymmetric...
CAR typically presents with subacute painless progressive bilateral (although asymmetry has been described) progressive vision loss over weeks to months, reflecting both rod and cone retinal dysfunction in most patients. Accordingly, symptoms often include nyctalopia (inability to see in dim light or at night), impaired dark adaptation, photopsia (flashes of light in the field of vision), photosensitivity, dyschromatopsia, and ultimately, severe visual acuity loss. Patients with CRMP-5-IgG-related ophthalmitis may have improvements with intra-ocular or systemic corticosteroid treatment. Patients with recoverin-related retinopathy are unlikely to have vision improvement with treatment.

**Useful For:** Evaluating patients with rapidly progressive vision loss where a paraneoplastic cause for vision loss (retinopathy or optic neuritis with other findings [e.g., retinitis] is suspected) Evaluating patients with small cell carcinoma who develop vision loss

**Interpretation:** Recoverin IgG: Seropositivity is consistent with a diagnosis of paraneoplastic retinopathy. Considerations include small cell carcinoma, pulmonary or extrapulmonary. Collapsin response-mediator protein-5 IgG: Seropositivity is consistent with a diagnosis of paraneoplastic retinitis or ophthalmitis. Considerations include small cell carcinoma, pulmonary or extrapulmonary.

**Reference Values:**

- **COLLAPSRN RESPONSE-MEDIATOR PROTEIN-5 TITER**
  - <1:240

- **RECOVERIN IMMUNOBLOT**
  - Negative

- **COLLAPSRN RESPONSE-MEDIATOR PROTEIN-5 WESTERN BLOT**
  - Negative

  Titters lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 1-800-533-1710 to request CRMP-5 Western blot. Neuron-restricted patterns of IgG staining that do not fulfill criteria for CRMP-5-IgG may be reported as "classified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, or sensory, sensorimotor, or autoimmune neuropathy, with or without a neuromuscular transmission disorder: Lambert-Eaton syndrome, myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

**Useful For:** Serological evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer. Directing a focused search for cancer. Investigating neurological symptoms that appear in the course of, or after, cancer therapy, and are not explainable by metastasis. Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy. Monitoring the immune response of seropositive patients in the course of cancer therapy. Detecting early evidence of cancer recurrence in previously seropositive patients.

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient’s immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

**Reference Values:**

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<th>Methodology</th>
<th>Reference value</th>
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<td>Amphiphysin Ab, S</td>
<td>Immunofluorescence (IFA)</td>
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<td>Anti-Glial Nuclear Ab, Type 1</td>
<td>IFA</td>
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<td>Anti-Neuronal Nuclear Ab, Type 1</td>
<td>IFA</td>
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**Reflex Tests:**

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PAC1 37430

**Paraneoplastic, Autoantibody Evaluation, Spinal Fluid**

**Clinical Information:** Several antineuronal and glial autoantibodies are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). Seropositive patients present with neurologic symptoms and signs in more than 90% of cases. The cancers are most commonly small-cell lung carcinoma, ovarian (or related mullerian) carcinoma, breast carcinoma, thymoma, or Hodgkin lymphoma. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures. Detection of the informative marker autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve survival. Serum is the preferred specimen for paraneoplastic autoantibodies. However, cerebrospinal fluid (CSF) results are sometimes positive when serum results are negative (especially for collapsin response-mediator protein-5-IgG [CRMP-5] and other inflammatory central nervous system autoimmunity). Additionally, CSF is more readily interpretable because it generally lacks the interfering nonorgan-specific antibodies that are common in the serum of patients with cancer. Because neurologists typically perform spinal taps in these patients, the recommendation is to submit CSF specimens with serum specimens, either for simultaneous testing or to be held for testing only if serum is negative. CRMP-5-IgG Western blot is also performed by specific request for more sensitive detection of CRMP-5-IgG. Testing should be requested in cases of subacute basal ganglionic disorders (chorea, Parkinsonism), cranial neuropathies (especially loss of vision, taste, or smell), and myelopathies.

**Useful For:** Aids in the diagnosis of paraneoplastic neurological autoimmune disorders related to carcinoma of lung, breast, ovary, thymoma, or Hodgkin lymphoma in spinal fluid specimens

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

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**Reflex Information:**

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<td>Radioimmunoassay (RIA)</td>
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<td>LGI1-IgG CBA, CSF</td>
<td>CBA</td>
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</tr>
<tr>
<td>GL1CC</td>
<td>mGluR1 Ab CBA, CSF</td>
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</tr>
<tr>
<td>GL1IC</td>
<td>mGluR1 Ab IFA, CSF</td>
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<tr>
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<td>mGluR1 Ab IFA Titer, CSF</td>
<td>IFA</td>
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<td>CBA</td>
<td>Negative</td>
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<tr>
<td>NMDIC</td>
<td>NMDA-R Ab IF Titer Assay, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
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<td>PCA-1 Immunoblot, CSF</td>
<td>IB</td>
<td>Negative</td>
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<tr>
<td>PCTBC</td>
<td>PCA-Tr Immunoblot, CSF</td>
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<tr>
<td>VGKCC</td>
<td>VGKC-complex Ab IPA, CSFRIA</td>
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</table>

Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, or CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable." Note: Titers lower than 1:2 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored spinal fluid (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 800-533-1710 to request CRMP-5 Western blot.

**Clinical References:** 1. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncological

**Parasite Identification, Varies**

**Clinical Information:** Infectious diseases are spread and caused by a variety of macroscopic vectors. A wide array of macroscopic parasites (worms and ectoparasites) and parasite mimics or artifacts may be submitted for examination and identification. It is important to promptly and accurately identify these specimens so that the ordering physician can appropriately treat and counsel the patient.

**Useful For:** Gross identification of parasites (eg, worms) and arthropods (eg, ticks, bed bugs, lice, mites) Detecting or eliminating the suspicion of parasitic infection by identifying suspect material passed in stool or found on the body Supporting the diagnosis of delusional parasitosis Identifying ticks, including Ixodes species (the vector for Lyme disease)

**Interpretation:** A descriptive report is provided identifying the worm or arthropod. Worms and hard ticks are identified to the species level when possible, while other parasitic arthropods are identified to the genus level. Arthropods that do not cause human disease and parasite mimics resembling worms are reported as nonparasites or free living insects.

**Reference Values:**
A descriptive report is provided.


**Parathyroid Hormone (PTH) Immunostain, Technical Component Only**

**Clinical Information:** Parathyroid hormone (PTH) staining is useful in identifying parathyroid glands in cases of hyperparathyroidism. Hyperproduction of parathyroid-like hormone may occur in association with lung tumors; such tumors may have reactivity with parathyroid hormone antibodies.

**Useful For:** Identification of parathyroid glands

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 1942

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**Parathyroid Hormone, Fine-Needle Aspiration Biopsy (FNAB)-Needle Wash**

**Clinical Information:** Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. PTH analysis in rinse material obtained from fine-needle aspiration biopsies (FNAB) has gained popularity to discriminate thyroid tissues from enlarged parathyroid glands and to also facilitate parathyroid localization prior to surgery. Various groups have reported on the utility of this technique with specificity of 91% to 100% and sensitivity of 82% to 100%. Measuring PTH in the rinse material proved to be very useful in cases of nondiagnostic cytology. Comparing the results of the PTH rinse material with serum PTH is highly recommended. An elevated PTH in the serum could falsely elevate PTH in the washings if the rinse is contaminated with blood. In these cases, only PTH values significantly higher than the serum should be considered as true positives. Cytologic examination and measurement of PTH can be performed on the same specimen. To measure PTH, the fine-needle aspirate (FNA) needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination has been expelled from the needle for a smear or CytoTrap preparation. Specimen collection is critical for the performance of the assay and the needle should be rinsed with a minimal volume. Each FNA needle from a single biopsied area is washed with 0.1 to 0.5 mL of normal saline. The washes from a single area are pooled (final volume 0.5-1.5 mL). PTH levels are measured in the saline wash.

**Useful For:** Discriminating thyroid tissue from enlarged parathyroid glands Facilitating parathyroid localization prior to surgery An adjunct to cytology examination of fine-needle aspiration specimens to confirm or exclude presence of parathyroid tissue in the biopsied area.

**Interpretation:** Parathyroid hormone (PTH) values less than 100 pg/mL suggest the biopsied site does not contain PTH-secreting tissue. PTH values greater than or equal to 100 pg/mL are suggestive of the presence PTH-secreting tissue at the site biopsied or along the needle track. This result is dependent on accurate sampling and a total needle wash volume between 0.5 and 1.5 mL. This test should be interpreted in the context of the clinical presentation, imaging, and cytology findings. If the results are discordant with the clinical presentation, a sampling error at the time of the biopsy should be considered.

**Reference Values:** An interpretive report will be provided.


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**Parathyroid Hormone, Serum**

**Clinical Information:** Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. The hormone is synthesized as a 115-amino acid precursor (pre-pro-PTH), cleaved to pro-PTH, and then to the 84-amino acid molecule, PTH (numbering, by universal convention, starting at the amino terminus). The precursor
forms generally remain within the parathyroid cells. Secreted PTH undergoes cleavage and metabolism to form carboxyl-terminal fragments (PTH-C), amino-terminal fragments (PTH-N), and mid-molecule fragments (PTH-M). Only those portions of the molecule that carry the amino-terminus (ie, the whole molecule and PTH-N) are biologically active. The active forms have half-lives of approximately 5 minutes. The inactive PTH-C fragments, with half-lives of 24 to 36 hours, make up more than 90% of the total circulating PTH and are primarily cleared by the kidneys. In patients with renal failure, PTH-C fragments can accumulate to very high levels. PTH 1-84 is also elevated in these patients, with mild elevations being considered a beneficial compensatory response to end organ PTH resistance, which is observed in renal failure. The serum calcium level regulates PTH secretion via negative feedback through the parathyroid calcium sensing receptor (CASR). Decreased calcium levels stimulate PTH release. Secreted PTH interacts with its specific type II G-protein receptor, causing rapid increases in renal tubular reabsorption of calcium and decreased phosphorus reabsorption. It also participates in long-term calciostatic functions by enhancing mobilization of calcium from bone and increasing renal synthesis of 1,25-dihydroxy vitamin D, which, in turn, increases intestinal calcium absorption. In rare inherited syndromes of parathyroid hormone resistance or unresponsiveness, and in renal failure, PTH release may not increase serum calcium levels. Hyperparathyroidism causes hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. Long-term consequences are dehydration, renal stones, hypertension, gastrointestinal disturbances, osteoporosis, and sometimes neuropsychiatric and neuromuscular problems. Hyperparathyroidism is most commonly primary and caused by parathyroid adenomas. It can also be secondary in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in renal failure. Long-standing secondary hyperparathyroidism can result in tertiary hyperparathyroidism, which represents the secondary development of autonomous parathyroid hypersecretion. Rare cases of mild, benign hyperparathyroidism can be caused by inactivating CASR genetic variants. Hypoparathyroidism is most commonly secondary to thyroid surgery, but can also occur on an autoimmune basis, or due to activating CASR genetic variants. The symptoms of hypoparathyroidism are primarily those of hypocalcemia, with weakness, tetany, and possible optic nerve atrophy.

**Useful For:** Diagnosis and differential diagnosis of hypercalcemia Diagnosis of primary, secondary, and tertiary hyperparathyroidism Diagnosis of hypoparathyroidism Monitoring end-stage renal failure patients for possible renal osteodystrophy

**Interpretation:** About 90% of the patients with primary hyperparathyroidism have elevated parathyroid hormone (PTH) levels. The remaining patients have normal (inappropriate for the elevated calcium level) PTH levels. About 40% of the patients with primary hyperparathyroidism have serum phosphorus levels below 2.5 mg/dL, and about 80% have serum phosphorus below 3.0 mg/dL. A (appropriately) low PTH level and high phosphorus level in a hypercalcemic patient suggests that the hypercalcemia is not caused by PTH or PTH-like substances. A (appropriately) low PTH level with a low phosphorus level in a hypercalcemic patient suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid-related peptide (PTHRP). PTHRP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types. A low or normal PTH in a patient with hypocalcemia suggests hypoparathyroidism, provided the serum magnesium level is normal. Low magnesium levels inhibit PTH release and action and can mimic hypoparathyroidism. Low serum calcium and high PTH levels in a patient with normal renal function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bio-ineffective PTH. A limited number of the PTH-C fragments, which accumulate in renal failure, chiefly PTH 7-84, cross-react in this and other intact PTH assays. PTH 1-84 is also elevated in renal failure, with mild elevations being considered beneficial. Consequently, when measured with an intact PTH assay, concentrations of 1.5 to 3 times the upper limit of the healthy reference range appear to represent the optimal range for end-stage renal failure patients. Lower concentrations may be associated with adynamic renal bone disease, while higher levels suggest possible secondary or tertiary hyperparathyroidism, which can result in high-turnover renal osteodystrophy. Some patients with moderate hypercalcemia and equivocal phosphate levels, who have either mild elevations in PTH or (inappropriately) normal PTH levels, may be suffering from familial hypocalciuric hypercalcemia, which is due to inactivating CASR genetic variants. The molar renal calcium to creatinine clearance is typically less than 0.01 in these individuals. The condition can be confirmed by CASR gene sequencing; see CASRZ / CASR Gene, Full Gene Analysis, Varies.

**Reference Values:**

<1 month: 7.0-59 pg/mL
**Clinical References:**

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**Parathyroid Hormone-Related Peptide, Plasma**

**Clinical Information:** Parathyroid hormone-related peptide (PTHrP) exists in several isoforms, ranging in size from 60 to 173 amino acids, which are created by differential splicing and post-translational processing by prohormone convertases. PTHrP is produced in low concentrations by virtually all tissues. The N-terminus and the secondary structure of multiple isoforms of PTHrP resemble parathyroid hormone (PTH), allowing PTHrP to bind to the same receptor as PTH. The physiological role of PTHrP can be divided into 5 categories: 1) transepithelial calcium transport, particularly in the kidney and mammary gland; 2) smooth muscle relaxation in the uterus, bladder, gastrointestinal tract, and arterial wall; 3) regulation of cellular proliferation; 4) cellular differentiation and apoptosis of multiple tissues; and 5) as an indispensable component of successful pregnancy and fetal development (embryonic gene deletion is lethal in mammals). Hypercalcemia of malignancy (HHM) is a common complication of cancer. Elevations of PTHrP are the most common cause of malignancy-associated hypercalcemia. PTHrP leads to hypercalcemia by stimulating calcium resorption from bone and reabsorption in the kidneys. It also plays a significant function in osteolysis in bony metastases, particularly in breast cancer, and has been postulated to play a role in malignancy-associated cachexia through induction of orexigenic peptides. Various malignancies secrete PTHrP resulting in HHM. PTHrP production is most commonly seen in carcinomas of breast, lung (squamous), head and neck (squamous), kidney, bladder, cervix, uterus, and ovary. Neuroendocrine tumors may also occasionally produce PTHrP. Most other carcinomas, sarcomas, and hematolymphatic malignancies only sporadically produce PTHrP, with the exception of T-cell lymphomas and myeloma. In HHM, the typical laboratory presentation includes elevated calcium (Ca) and PTHrP, decreased PTH, and suppressed serum 1,25 dihydroxyvitamin D3 levels. Patients with HHM may have increased PTHrP values before treatment. PTHrP level decreases and PTH level increases, accompanied by decreased serum calcium values, are observed with successful treatment.

**Useful For:** Aiding in the evaluation of patients with hypercalcemia of unknown origin. Aiding in the evaluation of patients with suspected humoral hypercalcemia of malignancy. The test should not be used to exclude cancer or screen tumor patients for humoral hypercalcemia of malignancy.

**Interpretation:** Depending on the patient population, up to 80% of patients with malignant tumors and hypercalcemia will be suffering from humoral hypercalcemia of malignancy (HHM). Of these, 50%
to 70% might have an elevated parathyroid hormone-related peptide (PTHrP) level. These patients will also usually show typical biochemical changes of excess parathyroid hormone (PTH)-receptor activation, namely, besides the hypercalcemia, they might have hypophosphatemia, hypercalcuria, hyperphosphaturia, and elevated serum alkaline phosphatase. Their PTH levels will typically be less than 30 pg/mL or undetectable. In patients with biochemical findings that suggest, but do not prove, primary hyperparathyroidism (eg, hypercalcemia, but normal or near-normal serum phosphate, and a PTH level that is within the population reference range but above 30 pg/mL), HHM should be considered as a diagnostic possibility, particularly if the patient is elderly, has a history of malignancy, or risk factors for malignancy. An elevated PTHrP level in such a patient is highly suggestive of HHM as the cause for the hypercalcemia.

**Reference Values:**
< 4.2 pmol/L

**Clinical References:**

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**PPAP 52964**

**Parental Sample Prep for Prenatal Microarray Testing, Blood**

**Clinical Information:** In order to interpret equivocal array results on a prenatal sample (amniotic fluid or chorionic villus), parental studies are performed to determine if the abnormality detected on the prenatal array is inherited or de novo. Maternal cell contamination testing is performed on the maternal blood and prenatal sample to detect the presence of maternal cells in the fetal sample.

**Useful For:** Preparing parental blood samples for possible confirmation testing if an abnormality is detected on the prenatal array sample DNA extraction of the maternal blood sample used for maternal cell contamination testing

**Interpretation:** No interpretation will be provided. This test is for sample processing only.

**Reference Values:**
An interpretive report will be provided.

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**PCAB 83728**

**Parietal Cell Antibodies, IgG, Serum**

**Clinical Information:** Pernicious anemia (PA) is a common form of cobalamin (vitamin B12) deficiency anemia.(1) The disorder is characterized by abnormally large (megablastic) red blood cells and atrophic body gastritis (ABG) resulting from autoimmune-mediated destruction of parietal cells that line the stomach wall. The destruction of parietal cells leads to impaired production of intrinsic factor (IF) required for the absorption of vitamin B12. PA is frequently associated with other autoimmune conditions such as autoimmune thyroid disease, type 1 diabetes mellitus, and vitiligo.(2-5) Diagnosis of PA relies on histologically proven ABG, peripheral blood examination showing megaloblastic anemia, vitamin B12 deficiency, parietal cell antibodies (PCA) with or without intrinsic factor antibodies (IFA), and elevated serum gastrin from loss of acid secretion.(2-4) PCA bind to the alpha- and beta-subunits of the membrane-bound H(+)/K(+)-ATPase while IFA bind directly to intrinsic factor, blocking its ability to bind vitamin B12.(1,4) Both PCA and IFA are useful diagnostic tests for PA, however, compared to PCA, IFA are more specific and lack diagnostic sensitivity.(2,4,5)

**Useful For:** Evaluating patients suspected of having pernicious anemia or autoimmune-mediated deficiency of vitamin B12 with or without megaloblastic anemia

**Interpretation:** A positive result indicates the presence of IgG antibodies to H(+)K(+) ATPase and maybe suggestive of pernicious anemia (PA) or a related autoimmune disease. A negative result indicates no detectable IgG antibodies to H(+)/K(+) ATPase; it does not rule out PA. An equivocal result is inconclusive for the presence of IgG antibodies to H(+)/K(+)ATPase. Consider re-testing in 4-6 weeks if
clinical suspicion for PA is high.

**Reference Values:**
Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units
Reference values apply to all ages.


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**Parietaria judaica, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Parietaria judaica Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Parietaria officinalis, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Parietaria officinalis Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


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**Paroxetine, Serum**

**Clinical Information:** Paroxetine (Paxil and Paxil CR) is approved for treatment of depression. Paroxetine is completely absorbed. Metabolites of paroxetine are inactive. Paroxetine metabolism is carried out by cytochrome P450 (CYP) 2D6. Paroxetine can saturate CYP2D6 resulting in a nonlinear relationship between dose and serum concentration. Paroxetine clearance is significantly affected by reduced hepatic function, but only slightly by reduced renal function. A typical adult paroxetine dose is 30 mg per day. Paroxetine is 100% bioavailable, 95% protein bound, and the apparent volume of distribution is 17 L/Kg. Time to peak serum concentration is 5 hours for the regular product and 8 hours for the controlled release product. The elimination half-life is 20 hours. Half-life is prolonged in the elderly and with cirrhosis.
Useful For: Monitoring paroxetine therapy Identifying noncompliance, although regular blood level monitoring is not indicated in most patients Identifying states of altered drug metabolism when used in conjunction with CYP2D6 genotyping

Interpretation: Steady-state serum concentrations associated with optimal response to paroxetine are in the range of 30 to 120 ng/mL and in the narrower range of 20 to 65 ng/mL. The most common toxicities associated with excessive serum concentration are asthenia, anticholinergic effects, anxiety, blurred vision, and changes in sexual function. The toxic range for paroxetine is greater than 120 ng/mL.

Reference Values: 30-120 ng/mL


Paroxysmal Nocturnal Hemoglobinuria, PI-Linked Antigen, Blood

Clinical Information: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disorder characterized by nocturnal hemoglobinuria, chronic hemolytic anemia, thrombosis, pancytopenia, and, in some patients, acute or chronic myeloid malignancies. PNH appears to be a hematopoietic stem cell disorder that affects erythroid, granulocytic, and megakaryocytic cell lines. The abnormal cells in PNH have been shown to lack glycosylphosphatidylinositol (GPI)-linked proteins in erythroid, granulocytic, megakaryocytic, and, in some instances, lymphoid cells. Variants in the phosphatidylinositol glycan A gene, PIGA, have been identified consistently in patients with PNH, thus confirming the biological defect in this disorder. A flow cytometric-based assay can detect the presence or absence of these GPI-linked proteins in granulocytes, monocytes, erythrocytes, and lymphocytes, thus avoiding the problems associated with red blood cell (RBC)-based diagnostic methods (Ham test) in which recent hemolytic episodes or recent transfusions can give false-negative results. A partial list of known GPI-linked proteins include CD14, CD16, CD24, CD55, CD56, CD58, CD59, C8-binding protein, alkaline phosphatase, acetylcholine esterase, and a variety of high frequency human blood antigens. In addition, fluorescent aerolysin (FLAER) binds directly to the GPI anchor and can be used to evaluate the expression of the GPI linkage.

Useful For: Screening for and confirming the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) Monitoring patients with PNH

Interpretation: Individuals with paroxysmal nocturnal hemoglobinuria (PNH) have absent or decreased expression of all the glycosylphosphatidylinositol (GPI)-linked antigens and fluorescent aerolysin (FLAER) on peripheral blood cells derived from the PNH clone. Recent data showed that small PNH clones can be detected in a relatively high percentage of cases of aplastic anemia and myelodysplastic syndrome. While the significance of this finding is still uncertain, it appears that these patients may benefit from immunosuppressive therapy. This test incorporates a sophisticated technique of separating different cell populations using gating on antigen-positive cells, as well as the sensitivity
to enable detection of small PNH clones. In addition, this test detects a partial loss of CD59 on RBCs (type II RBC). Patients with large proportion of type II RBC are unlikely to show high levels of hemolysis, unlike patients with complete loss of GPI-linked proteins (predominantly type III cells). While PNH is a disorder of hematopoietic stem cells and all lineages are affected, the percentage of affected cells can differ between lineages, most commonly due to RBC hemolysis and/or transfusion. Individuals without PNH have normal expression of FLAER (neutrophils and monocytes) and normal expression of all GPI-linked antigens-CD14 (monocytes), CD16 (neutrophils and NK cells), CD24 (neutrophils), and CD59 (RBCs).

Reference Values:
An interpretive report will be provided.

RED BLOOD CELLS:
PNH RBC-Partial Antigen loss: 0.00-0.99%
PNH RBC-Complete Antigen loss: 0.00-0.01%
PNH Granulocytes: 0.00-0.01%
PNH Monocytes: 0.00-0.05%

Clinical References:

Parrot Australian (Budgerigar) Feathers IgE

Interpretation: Class IgE (kU/L) Comment
<0.10 Negative 0/1 0.10 Åêâ,¬åêç 0.34
Equivocal/Borderline 1 0.35 Åêâ,¬åêç 0.69 Low Positive 2 0.70 Åêâ,¬åêç 3.49 Moderate Positive 3 3.50 Åêâ,¬åêç 17.49 High Positive 4 17.50 Åêâ,¬åêç 49.99 Very High Positive 5 50.00 Åêâ,¬åêç 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

Parsley IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related
complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as
evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.
This test should only be ordered by physicians who recognize the limitations of the test.

**PSLY 82765**

**Parsley, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
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bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to parsley Defining the allergen responsible for
eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or
anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the
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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
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<td>17.5-49.9</td>
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<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry’s
Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,

**PPPC 113354**

**Particle Preparation (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.
Parvovirus B19 Antibodies, IgG and IgM, Serum

Clinical Information: Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, day care centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life, and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

Useful For: Serologic detection of recent or past parvovirus B19 infection

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to Parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

Reference Values:
IgG: Negative
IgM: Negative

Clinical References:
assay testing.

**Useful For:** Serologic detection of recent or past parvovirus B19 infection using IgG antibodies This test is not useful as a screening procedure for the general population

**Interpretation:** Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative, or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

**Reference Values:**
Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

**Negative**

**Clinical References:**

**PARVM 48321**

**Parvovirus B19 Antibody, IgM, Serum**

**Clinical Information:** Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, day care centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells. Infection with parvovirus B19 occurs early in life, and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

**Useful For:** Serologic detection of recent or past parvovirus B19 infection using IgM antibodies This test is not useful as a screening procedure for the general population

**Interpretation:** Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative, or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach
peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

**Reference Values:**
Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

**Clinical References:**

**PARVN**

**Parvovirus B19 Antibody, Technical Interpretation**

**Clinical Information:** Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, day care centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells. Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

**Useful For:** Interpretation of serologic testing for recent or past parvovirus B19 infection. This test is not useful as a screening procedure for the general population.

**Interpretation:** Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

**Reference Values:**
Only orderable as part of a profile. For further more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

IgG: Negative
IgM: Negative

**Clinical References:**
3. Summers J, Jones SE, Anderson MJ: Characterization of the genome of the agent

**PARVP 86337**

**Parvovirus B19, Molecular Detection, PCR, Plasma**

**Clinical Information:** Parvovirus B19 is a DNA virus that preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 can occur at any age, but is most common early in life. Antibody prevalence ranges from 2% to 15% in children 1 to 5 years old to 30% to 60% in adults.(1) The virus is transmitted by respiratory secretions and occasionally by blood products. Parvovirus B19 infections can be asymptomatic or produce a wide spectrum of disease ranging from erythema infectiosum (“fifth disease” characterized by a classic “slapped cheek” rash) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host.(2,3) Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, spontaneous abortion, or stillbirth of the fetus.(4) Parvovirus B19 is also the causative agent of transient aplastic crisis and chronic aplasia usually, but not exclusively, in immunocompromised or transplant patients, and those with preexisting hematologic disorders (eg, sickle cell disease). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG- and IgM-class antibodies with enzyme-linked immunosorbent assay testing.

**Useful For:** Diagnosing parvovirus B19 infection in plasma specimens

**Interpretation:** A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

**Reference Values:**
Not applicable


**PARVO 83151**

**Parvovirus B19, Molecular Detection, PCR, Varies**

**Clinical Information:** Parvovirus B19 is a DNA virus that preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 can occur at any age, but is most common early in life. Antibody prevalence ranges from 2% to 15% in children 1 to 5 years old to 30% to 60% in adults.(1) The virus is transmitted by respiratory secretions and occasionally by blood products. Parvovirus B19 infections can be asymptomatic or produce a wide spectrum of disease ranging from erythema infectiosum (“fifth disease” characterized by a classic “slapped cheek” rash) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host.(2,3) Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, spontaneous abortion, or stillbirth of the fetus.(4) Parvovirus B19 is also the causative agent of transient aplastic crisis and chronic aplasia usually, but not exclusively, in immunocompromised or transplant patients, and those with preexisting hematologic disorders (eg, sickle cell disease). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG- and IgM-class antibodies with enzyme-linked immunosorbent assay testing.

**Useful For:** Diagnosing parvovirus B19 infection
Interpretation: A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

Reference Values:
Negative

Clinical References:

Parvovirus Immunostain, Technical Component Only

Clinical Information: Parvovirus infection is implicated as a cause of hydrops fetalis and may result in spontaneous abortions. It has also been implicated in chronic hemolytic anemia. The virus is associated with erythema infectiosum (Fifth disease) in children and acute arthritis in adults.

Useful For: Identification of parvovirus infection

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

Passion Fruit, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing the diagnosis of an allergy to passion fruit. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>0</td>
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<td>Negative</td>
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<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
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<td>3.50-17.4</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


PATHC 70317

Pathology Consultation

Clinical Information: Mayo Clinic in Rochester, MN is staffed by pathologists whose expertise and special interests cover the entirety of pathology—from surgical pathology with all of its respective subspecialty areas, to Hematopathology, Renal Pathology, and Dermatopathology. Consultation services are provided for difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and sometimes transferred between the pathologists, as deemed appropriate for the type of case or diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Stained slides and paraffin blocks received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (e.g., cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. The goal is to provide the highest possible level of diagnostic consultative service, while balancing optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

Useful For: Obtaining an expert second opinion on specimens referred by the primary pathologist. Obtaining special studies not available locally. This test is not intended to be used to obtain a primary diagnosis.

Interpretation: Results of the consultation are reported in a formal pathology report that includes a
description of ancillary test results (if applicable) and an interpretive comment. The consultative practice strives to bring the client the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner with a rapid turnaround time for diagnostic results.

Reference Values:
The laboratory will provide a pathology consultation.

PAX5
70533

PAX-5 Immunostain, Technical Component Only

Clinical Information: PAX-5, also known as B-cell-specific activator protein (BSAP), is a B-cell specific transcription factor expressed during differentiation. Plasma cells (terminally differentiated B cells) are usually negative. Used in the classification of B-cell lymphomas.

Useful For: Classification of lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


PAX2
607795

PAX2 Immunostain, Technical Component Only

Clinical Information: Paired box gene 2 (PAX2) is a nuclear transcription factor. Expression of PAX2 and PAX8 is useful in the diagnosis of renal cell carcinoma. Loss of PAX2 expression is useful in the diagnosis of endocervical adenocarcinoma.

Useful For: Aids in the diagnosis of endocervical adenocarcinoma and renal cell carcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

PAX8 Immunostain, Technical Component Only

**Clinical Information:** PAX8 is a member of the paired box gene (PAX) family of transcription factors involved in kidney cell and thyroid development. PAX8 has been shown to be expressed in a high percentage of renal neoplasms, including both malignant renal cell carcinomas and benign renal tumors (oncocytomas). PAX8 has also been reported to be expressed in ovarian carcinomas.

**Useful For:** Aids in the identification of renal cell carcinomas, as well as papillary thyroid carcinomas and tumors of Mullerian origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

PCA3 (Prostate Cancer Antigen 3)

**Clinical Information:** Prostate cancer antigen 3 (PCA3, also known as Differential Display Code 3 or DD3) is a prostate-specific gene that was present in 95% of prostate cancer samples initially studied, and significantly over-expressed in cancer versus benign tissue. PCA3 is known to be a non-coding messenger ribonucleic acid (mRNA) with no resultant protein. Clinically, PCA3 mRNA is detectable in the urine and appears to be independent of prostate volume and serum PSA. The PCA3 urinary assay is reported out as a ratio of PCA3 mRNA to PSA mRNA.

**Reference Values:**
A score less than 25 is considered negative

A score greater than or equal to 25 is considered positive
**PDGF (22q13), Dermatofibrosarcoma Protuberans/Giant Cell Fibroblastoma, FISH, Tissue**

**Clinical Information:** Dermatofibrosarcoma protuberans (DFSP) is a superficial, low-grade sarcoma genetically characterized by the unbalanced chromosomal translocation t(17;22)(q21;q13), usually in the form of a supernumerary ring chromosome. The product of this chromosomal translocation is the chimeric gene COL1A1-PDGFB. Rearrangements of this gene have been detected in approximately 90% of DFSP and its related infantile form, giant cell fibroblastoma, but not in other tumors.

**Useful For:** Confirming the diagnosis of dermatofibrosarcoma protuberans (DFSP)/giant cell fibroblasto (GCF) and excluding other spindle neoplasms that closely simulate the DFSP histology, including dermatofibroma (benign fibrous histiocytoma), neurofibroma, spindle cell lipoma, and a variety of other benign and malignant spindle cell neoplasms.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the PDGFB FISH probe. A positive result is consistent with rearrangement/amplification of the PDGFB gene locus on 22q13 and supports the diagnosis of dermatofibrosarcoma protuberans (DFSP) or giant cell fibroblastoma (GCF). A negative result is consistent with no rearrangement/amplification of the PDGFB gene locus on 22q13. However, this result does not exclude the diagnosis of DFSP or GCF. The degree of PDGFB copy gain/amplification/rearrangement varies in individual tumors and among different cells in the same tumor. It is not currently known if patients with different levels of rearrangement/amplification have the same prognosis and response to therapy.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**PDGFRB/TEL Translocation (5;12) for Chronic Myelomonocytic Leukemia (CMML), FISH**

**Clinical Information:** Platelet-derived growth factor receptor-beta (PDGFRB) produces a tyrosine kinase involved in cell proliferation. Translocation-ets-leukemia protein (encoded by the gene ETV6) is a gene transcription protein that is frequently rearranged in leukemias. A 5;12 translocation, t(5;12)(q33;p13), results in a fusion product (PDGFRB/ETV6) that is seen in approximately 1% to 2% of patients diagnosed with chronic myelomonocytic leukemia. Patients with this translocation often have associated hypereosinophilia. Imatinib mesylate is an inhibitor of tyrosine kinases, including PDGFRB. Patients with the 5;12 translocation are reportedly responsive to imatinib mesylate; upon treatment, they usually go into complete remission.

**Useful For:** Identifying patients with chronic myelomonocytic leukemia and other hematologic disorders who may be responsive to imatinib mesylate Identifying and tracking chromosome abnormalities and response to therapy

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FBEP**

**Pea Black-Eyed/Cow Pea (Vigna sinensis) IgE**

**Interpretation:** Class IgE (kU/L) Comment

- 0 < 0.35 Below Detection
- 0.35 - 0.69 Low Positive
- 0.70 - 3.49 Moderate Positive
- 3.50 - 17.49 Positive
- 17.50 - 49.99 Strong Positive
- 50.00 - 99.99 Very Strong Positive
- > 99.99 Very Strong Positive

**Reference Values:**

< 0.35 kU/L

**FPGNG**

**Pea Green IgG**

**Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.

This test should only be ordered by physicians who recognize the limitations of the test.

**FPEAC**

**Peach IgG**

**Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question.

This test should only be ordered by physicians who recognize the limitations of the test.

**PECH**

**Peach, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to peach Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
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<td>0</td>
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<td>Negative</td>
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<tr>
<td>1</td>
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<td>17.5-49.9</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**FPNTG 57537**

**Peanut IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**FPNG4 57571**

**Peanut IgG4**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

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**PEANT 64756**

**Peanut, IgE with Reflex to Peanut Components, IgE, Serum**

**Clinical Information:** Peanut allergy is one of the most common food allergies in the United States, with an estimated prevalence of approximately 1% to 2%.(1) The clinical symptoms of peanut allergy may range from relatively mild, such as rhinorrhea, pruritus, or nausea, to a systemic and potentially
life-threatening anaphylactic reaction. The diagnosis of peanut allergy is dependent upon the presence of compatible clinical symptoms in the context of peanut exposure, with support from identification of potential peanut-specific IgE allergen antibodies, either by skin testing or in vitro serology testing. In vitro testing has generally focused on assessing for the presence of total peanut IgE antibodies. These antibodies are identified by immunoassay in which the capture allergen is an extract prepared from natural peanut raw material. Most studies have demonstrated a correlation between total peanut IgE allergen antibodies and an increased likelihood of a clinical allergic response. Once an elevated antibody response to total peanut IgE extract is established, assessment for the presence of specific IgE antibodies to the most common peanut allergenic components will be performed. During peanut component allergen testing the presence of IgE antibodies specific for potentially allergic individual proteins, namely Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, Ara h 9, and profilin protein Bet v2, are assessed. The determination of the relative amount of IgE antibody to specific peanut components can aid in assessment of the potential strength and type of allergenic response (see Table 1 below). Ara h 1, 2, 3, and 6 are seed storage proteins and are the most relevant for evaluation of suspected peanut allergy.(2,3) The presence of antibodies to Ara h 2, in particular, exhibits strong association with potential systemic reactions. Ara h 1, 2, and 3-specific IgE antibodies tend to be associated with more severe allergic reactions. Ara h6 shares substantial, but not complete, cross-reactivity with Ara h2, and often exhibits similarity in terms of the degree and type of allergenicity. Immunoglobulin E antibodies against Ara h 8 are generally associated with milder peanut allergies and may be seen in the context of birch pollen sensitization. Ara h 8 is a homologue of the birch pollen allergen Bet v1.(4) Ara h 9 is a member of the lipid transfer protein (LTP) family. LTP is ubiquitous throughout the plant kingdom and is also extremely homologous. IgE antibodies specific for Ara h 9 may be associated with allergic reactions upon peanut ingestion, although published data on this is not conclusive.(5) In addition, because of the significant sequence homology, cross-reactivity of IgE antibodies may be observed between Ara h 9 and LTP in commonly consumed plants such as peaches, apples, and plums. Finally, IgE antibodies to the profilin Bet v2, while associated with birch pollen sensitivity, also represent a minor peanut allergen marker as it is cross-reactive with the peanut profilin, Ara h5. As profilin proteins are present in many other foods, sensitivity to profilin Bet v2 may be associated in broad allergen cross-reactivity among foods, including mango, peach, apple, hazelnut, celery, carrot, paprika, anise, fennel, coriander, cumin, tomato, and potato. The presence of antibodies to profilin Bet v2 is typically associated with milder allergic reactions and oral allergy syndrome. Table of Specific Peanut Allergens

| Allergen        | Most common reaction type | Heat and digestion stability | Selected potential cross-reactivity with other allergens | Ara h1 (storage peanut protein) Systemic | Some potential allergenic cross reactivity with plant vicilins, including those found in soy and pea | Ara h2 (storage peanut protein) Systemic | Some potential allergenic cross reactivity with almond and brazil nut allergens | Ara h6 Ara h3 (storage peanut protein) Systemic | Some potential allergenic cross reactivity with hazelnut and soybean allergens | Ara h6 (storage peanut protein) Systemic | Strongly stable Ara h2 Ara h8 (PR-10 protein, Bet v 1-homologous allergen) Associated with local reactions such as oral allergy syndrome (OAS) | Labile to heat and digestion Associated with allergy to birch and birch related tree pollen | Ara h9 (lipid transfer protein) Associated with both systemic reactions and local reactions such as OAS Stable Associated with allergy to peach and peach related fruits | Profilin Bet v2 Associated with more minor local reactions such as OAS Labile to heat and digestion Associated with allergy to a broad variety of pollen and plant products from trees, nuts, grasses, and weeds |
|-----------------|--------------------------|-----------------------------|--------------------------------------------------------|---------------------------------|-----------------------------------------------|--------------------------------|-----------------------------------------------|---------------------------------|-----------------------------------------------|--------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Ara h1 (storage peanut protein) Systemic | Stable | Some potential allergenic cross reactivity with plant vicilins, including those found in soy and pea | Ara h2 (storage peanut protein) Systemic | Strongly stable | Some potential allergenic cross reactivity with almond and brazil nut allergens | Ara h6 Ara h3 (storage peanut protein) Systemic | Some potential allergenic cross reactivity with hazelnut and soybean allergens | Ara h6 (storage peanut protein) Systemic | Strongly stable | Ara h2 Ara h8 (PR-10 protein, Bet v 1-homologous allergen) Associated with local reactions such as oral allergy syndrome (OAS) | Labile to heat and digestion Associated with allergy to birch and birch related tree pollen | Ara h9 (lipid transfer protein) Associated with both systemic reactions and local reactions such as OAS Stable Associated with allergy to peach and peach related fruits | Profilin Bet v2 Associated with more minor local reactions such as OAS Labile to heat and digestion Associated with allergy to a broad variety of pollen and plant products from trees, nuts, grasses, and weeds |

**Useful For:** Evaluation of patients with suspected peanut allergy Evaluation of patients with possible peanut cross-reactivity

**Interpretation:** When detectable total peanut IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic peanut component IgE is detectable (> or =0.10 IgE kUa/L), an interpretative report will be provided. When the sample is negative for total peanut IgE antibody (<0.10 IgE kUa/L), further testing for specific peanut component IgE antibodies will not be performed. Negative IgE results for total peanut antibody may indicate a lack of sensitization to potential peanut allergenic components.

**Reference Values:**

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<tbody>
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</table>
0/1 0.10-0.34  Borderline / Equivocal
1 0.35-0.69  Equivocal
2 0.70-3.49  Positive
3 3.50-17.4  Positive
4 17.5-49.9  Strongly positive
5 50.0-99.9  Strongly positive
6 > or = 100  Strongly positive

Concentrations > or = 0.70 kU/L (Class 2 and above) will flag as abnormally high.

**Clinical References:**

**PEAN**

**PEAN 82888**

**Peanut, IgE, Serum**

**Clinical Information:** Peanut allergy is one of the most common food allergies in the United States, with an estimated prevalence of approximately 1% to 2%.(1) The clinical symptoms of peanut allergy may range from relatively mild, such as rhinorrhea, pruritus, or nausea, to a systemic and potentially life-threatening anaphylactic reaction. The diagnosis of peanut allergy is based upon the presence of compatible clinical symptoms in the context of peanut exposure, with support from identification of potential peanut-specific IgE allergen antibodies, either by skin testing or in vitro serology testing. In vitro serology testing has generally focused on assessing for the presence of total peanut IgE antibodies. These antibodies are identified by immunoassay in which the capture allergen is an extract prepared from natural peanut raw material. Most studies have demonstrated a correlation between the amount of total peanut IgE allergen antibody present and an increased likelihood of a clinical allergic response. Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. Once an elevated antibody response to total peanut IgE extract is established, assessment for the presence of specific IgE antibodies to the most common individual peanut allergenic components may be considered.

**Useful For:** Establishing a diagnosis of an allergy to peanut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

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</tr>
<tr>
<td>6</td>
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<td>Strongly positive</td>
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</table>

Concentrations > or =0.70 kU/L (Class 2 and above) will flag as abnormally high.

**Clinical References:**

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**Pear IgG**

**Interpretation:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Pear, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to pear Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tr>
<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages.


Pecan Food IgG

Interpretation:

Reference Values:

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Pecan Hickory, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to pecan hickory Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3 3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Pecan-Food, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pecan-food Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td></td>
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PAS38 83346

Pediatric Allergy Screen 3 to 8 Years, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pediatric allergy screen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>IgE kU/L</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
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Pediatric Allergy Screen

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pediatric allergy screen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class | IgE kU/L | Interpretation
--- | --- | ---
0 | 0 | Negative
1 | 0.35-0.69 | Equivocal
2 | 0.70-3.49 | Positive
3 | 3.50-17.4 | Positive
4 | 17.5-49.9 | Strongly positive
5 | 50.0-99.9 | Strongly positive
6 | > or =100 | Strongly positive Reference values apply to all ages.
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to pediatric allergy screen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
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**Pediatric Autoimmune Central Nervous System Disorders Evaluation, Serum**

**Clinical Information:** Autoimmune encephalitis and myelitis is increasingly recognized as a cause of central nervous system (CNS) disease in children and teens. N-methyl-D-aspartate receptor antibody (NMDA-R) encephalitis and myelin oligodendrocyte glycoprotein (MOG) autoimmunity are most common, though other entities, including aquaporin-4 autoimmunity, contactin-associated protein-like 2 (CASPR2) autoimmunity, autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, and paraneoplastic encephalomyelopathies, may also occur in children.

**Useful For:** Evaluating children with autoimmune central nervous system disorders using serum specimens

**Interpretation:** This profile is consistent with an autoimmune central nervous system disorder.

**Reference Values:**

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<td>PCA-2, S</td>
<td>IFA</td>
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<tr>
<td>PCABP</td>
<td>PCA-1, S</td>
<td>IFA</td>
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<tr>
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<td>Reporting Name</td>
<td>Methodology</td>
<td>Reference Value</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>GL1IC</td>
<td>mGluR1 Ab IFA, CSF</td>
<td>IFA</td>
<td>Negative</td>
</tr>
<tr>
<td>LG1CC</td>
<td>LGI1-IgG CBA, CSF</td>
<td>CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>NMDCC</td>
<td>NMDA-R Ab CBA, CSF</td>
<td>CBA</td>
<td>Negative</td>
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<tr>
<td>NMOFC</td>
<td>NMO/AQP4 FACS, CSF</td>
<td>Fluorescence-Activated Cell Sorting Assay (FACS)</td>
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<tr>
<td>PCTRC</td>
<td>Purkinje Cell Cytoplasmic AbIFA Type Tr</td>
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<th>Methodology</th>
<th>Reference Value</th>
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<tr>
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<tr>
<td>AGNBC</td>
<td>AGNA-1 Immunoblot, CSF</td>
<td>Immunoblot (IB)</td>
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<tr>
<td>AMIBC</td>
<td>Amphiphysin Immunoblot, CSF</td>
<td>IB</td>
<td>Negative</td>
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<tr>
<td>AMPCC</td>
<td>AMPA-R Ab CBA, CSF</td>
<td>CBA</td>
<td>Negative</td>
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<tr>
<td>AMPHC</td>
<td>Amphiphysin Ab, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>AMPIC</td>
<td>AMPA-R Ab IF Titer Assay, CSF</td>
<td>IFA</td>
<td>Negative</td>
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<tr>
<td>ANN2C</td>
<td>Anti-Neuronal Nuclear Ab, Type 2</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>AN1BC</td>
<td>ANNA-1 Immunoblot, CSF</td>
<td>IB</td>
<td>Negative</td>
</tr>
<tr>
<td>AN2BC</td>
<td>ANNA-2 Immunoblot, CSF</td>
<td>IB</td>
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</tr>
<tr>
<td>ANN3C</td>
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<td>IFA</td>
<td></td>
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<tr>
<td>DPPCC</td>
<td>DPPX Ab CBA, CSF</td>
<td>CBA</td>
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</tr>
<tr>
<td>DPPTC</td>
<td>DPPX Ab IFA Titer, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>GABIC</td>
<td>GABA-B-R Ab IF Titer Assay, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>GFACC</td>
<td>GFAP CBA, CSF</td>
<td>CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>GFATC</td>
<td>GFAP IFA Titer, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>GL1CC</td>
<td>mGluR1 Ab CBA, CSF</td>
<td>CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>GL1TC</td>
<td>mGluR1 Ab IFA Titer, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>NMDIC</td>
<td>NMDA-R Ab IF Titer Assay, CSF</td>
<td>IFA</td>
<td></td>
</tr>
<tr>
<td>NMOTC</td>
<td>NMO/AQP4 FACS Titer, CSF</td>
<td>FACS</td>
<td></td>
</tr>
<tr>
<td>PC1BC</td>
<td>PCA-1 Immunoblot, CSF</td>
<td>IB</td>
<td>Negative</td>
</tr>
<tr>
<td>PCA1C</td>
<td>Purkinje Cell Cytoplasmic Ab IFA Type 1</td>
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<td></td>
</tr>
<tr>
<td>PCA2C</td>
<td>Purkinje Cell Cytoplasmic Ab IFA Type 2</td>
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</tbody>
</table>
Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, ANNA-3, PCA-1, PCA-2, or PCA-Tr may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References:

Penicillin G, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to penicillin G Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>
Penicillin V, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to penicillin V Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Penicillium chrysogenum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Penicillium chrysogenum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
<td></td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Pentobarbital, Serum

Clinical Information: Pentobarbital is a short-acting barbiturate with anticonvulsant and sedative-hypnotic properties. Uses include sedation induction; relief of preoperative anxiety; control of status epilepticus or seizures resulting from meningitis, tetanus, alcohol withdrawal, poisons, chorea, or eclampsia; and induction of coma in the management of cerebral ischemia and increased intracranial pressure that may follow stroke or head trauma.(1,2) Pentobarbital is administered orally, parenterally, and rectally. The duration of hypnotic effect is about 1 to 4 hours. The drug distributes throughout the body with about 35% to 45% of a dose bound to plasma proteins in the blood. Metabolism takes place in the liver via oxidation to the inactive metabolite, hydroxypentobarbital. Elimination is biphasic; half-life is about 4 hours in the first phase, and 35 to 50 hours in the second phase. Excretion occurs through the
urine, mainly as glucuronide conjugates of metabolites, with only about 1% excreted as unchanged drug. (1,2) Tolerance to the hypnotic effects of pentobarbital occurs after about 2 weeks of continuous dosing.

**Useful For:** Monitoring of pentobarbital therapy treatment

**Interpretation:** Pentobarbital concentrations above 10 mcg/mL have been associated with toxicity.

**Reference Values:**
- Therapeutic range
  - Hypnotic: 1-5 mcg/mL
  - Therapeutic coma: 20-50 mcg/mL
  - Reducing intracranial pressure: 30-40 mcg/mL
- This degree of sedation requires artificial respiratory support.
- Toxic concentration: >10 mcg/mL

**Clinical References:**
1. NEMBUTAL Sodium Solution (pentobarbital sodium injection). Package insert: Ovation Pharmaceuticals Inc; October 2007

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**FPBPG**

**Pepper Bell/Paprika IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**FPBLG**

**Pepper Black IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**FPCYE**

**Pepper Cayenne (Capsicum frutescens) IgE**

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.35 Below Detection
1 0.35 - 0.69 Low Positive
2 0.70 - 3.49 Moderate Positive
3 3.50 - 17.49 Positive
4 17.50 - 49.99 Strong Positive
5 50.00 - 99.99 Very Strong Positive
6 >99.99 Very Strong Positive

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Reference Values:
<0.35 kU/L

**FPCHI 57664 Pepper Chili IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FPEPA 57838 Pepsin A Assay**

**Reference Values:**
Protein Unit = mg/mL
One unit of pepsin A = 0.1 ng/mL
Pepsin A by Elisa assay

Pepsin A Reference Range (Units):
<3.0 negative
3-50 weak to moderate positive
>50 strong positive

**FPEPS 91638 Pepsinogen I**

**Reference Values:**
28 - 100 ng/mL
(mean 40)

**FPERP 75385 Perampanel, Serum**

**Interpretation:** Daily administration of 6 mg perampanel resulted in peak plasma concentrations averaging 460 ng/mL at approximately 1.3 hours post dose. Peak concentrations following a single 12 mg dose of perampanel averaged 800 ng/mL.

**Reference Values:**
Reporting limit determined each analysis.
Units: ng/mL

**FOPE 57938 Perch Ocean**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Å–0.69 Low Positive 2 0.70 Å–3.49 Moderate Positive 3 3.50 Å–17.49 Positive 4 17.50 Å–49.99 Strong Positive 5 50.00 Å–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L
**Percocet, Urine**

**Reference Values:**

Percocet, Urine:

Acetaminophen: ug/mL

Note: Analysis performed on urine.

Reference ranges have not been established for urine specimens.

Oxycodone: ng/mL
Oxymorphone: ng/mL

**Peripheral Blood (Bill Only)**

**Reference Values:**

This test is for billing purposes only.
This is not an orderable test.

**Peripheral Blood, TC (Bill Only)**

**Reference Values:**

This test is for billing purposes only.
This is not an orderable test.

**Peripheral Nerve Pathology Consultation**

**Clinical Information:** Nerve biopsies provide information about nerve fibers and the interstitium of the nerve. Neuropathic abnormalities include decreased density of myelinated fibers, segmental demyelination, and axonal degeneration. Some possible interstitial abnormalities that affect nerves include necrotizing vasculitis and amyloidosis. This consultation is for fixed tissue, slides, or blocks.

**Useful For:** Evaluating diseases of the nerve and disorders that affect nerve function

**Interpretation:** The clinical and neurological history is reviewed with the interpretation of the biopsy. The histologic slides, special stains, and history, along with the physician's report are correlated by a neuromuscular pathologist. An interpretive report will be provided.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


**Peripheral Neuropathy Genetic Panels, Next-Generation Sequencing (NGS), Blood**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common diverse group of
disorders with heterogeneous genetic causes. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Additionally, peripheral neuropathy may be part of an inherited systemic syndromic or metabolic disorder caused by genes in metabolic pathways. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement: 1. Hereditary motor and sensory neuropathy (HMSN), also referred as Charcot Marie Tooth (CMT) 2. Hereditary sensory and autonomic neuropathy (HSAN) or hereditary sensory neuropathy (HSN), if autonomic dysfunction is absent 3. Distal hereditary motor neuropathy (dHMN) Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as in hereditary spastic paraplegia (HSP) with neuropathy (complicated form, also referred to as HMSN type 5) or be part of a systemic syndromic or metabolic disorder. Hereditary Motor and Sensory Neuropathy: HMSN, or CMT disease, is a major category of inherited peripheral neuropathies and is the most commonly inherited neuromuscular disorder. It is characterized by motor or sensory peripheral nerve involvement. The clinical phenotype is variable and includes wasting and weakness of the distal limb muscles, skeletal deformities, and hearing loss. HMSN/CMT is classified into 5 groups: 1. HMSN 1, which is a dominantly inherited demyelinating form 2. HMSN 2, a dominantly inherited axonal predominant neuropathy 3. HMSN 3 (also called Dejerine-Sottas disease), which is often inherited dominantly with onset in infancy or childhood, is characterized by extremely slow nerve conduction velocities resulting in loss of ambulatory milestones and more generalized neurologic deficit 4. HMSN 4, an autosomal recessive inherited demyelinating form that may also present with extraneural features, including facial dysmorphism and scoliosis, particularly those with HMSN 4C, the most frequent form of HMSN 4 5. HMSN 5, a form associated with spasticity, also known as "complex hereditary spastic paraplegia (HSP)" Hereditary Motor Neuropathy: dHMN are one of the major categories of peripheral inherited neuropathies and are characterized by length-dependent, slowly progressive motor neuropathies with variable nerve conduction velocities. The clinical phenotype is variable but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. There is significant phenotypic overlap with HMSN/CMT; however, sensory loss is usually absent in dHMN. dHMN are subdivided into 11 subtypes based on inheritance pattern and clinical features, and include types 1-7, dHMN plus pyramidal signs, X-linked, congenital distal spinal muscular atrophy, and Jerash type. Hereditary Sensory and Autonomic Neuropathy: HSAN, or HSN if autonomic dysfunction is absent, are one of the major categories of inherited peripheral neuropathies. They affect sensory and autonomic nerves and the hallmark feature is the presence of prominent small-fiber involvement. HSAN are subdivided into 5 groups based on age of onset, inheritance pattern, and clinical features: 1. HSAN 1 varieties (HSAN 1A-E) follow an autosomal dominant inheritance pattern with juvenile or adult onset, and severe sensory loss and autonomic dysfunction 2. HSAN 2-5 have an autosomal recessive inheritance pattern and are usually congenital 3. HSAN 3, also known as familial dysautonomia or Riley-Day syndrome, is characterized by prominent autonomic and small-fiber sensory involvement 4. HSAN 4 and 5 are characterized by insensitivity to pain and widespread autonomic disturbance, with HSAN 4 also featuring mental retardation. Hereditary Spastic Paraplegia: HSP is characterized by progressive lower extremity weakness and spasticity, and may present with prominent peripheral neuropathy as one of the complicated forms, also known as HMSN type 5. The complicated forms are associated with a variety of other neurological systemic abnormalities and usually follow an autosomal recessive inheritance pattern. The uncomplicated or pure form presents with lower limb weakness and spasticity, and is predominantly characterized by an autosomal dominant inheritance pattern. SEPT9 Gene, Full Gene Analysis: Hereditary neuralgic amyotrophy (HNA) is an autosomal dominant disorder characterized by periods of severe pain involving the brachial plexus followed by muscle atrophy and weakness. These recurrent episodes can also be accompanied by decreased sensation and paresthesias. Individuals with this disease are generally symptom-free between pain attacks, though many experience lingering effects with repeated attacks. The pain episodes are frequently triggered by physical, emotional, or immunological stress. Less commonly, affected individuals can exhibit non-neurological features including short stature, skin folds, hypotelorism, and cleft palate. Variants in the SEPT9 gene cause the clinical manifestations of HNA. SEPT9 is currently the only known gene associated with HNA, although approximately 15% of HNA families do not show linkage to this gene. Given the considerable phenotypic overlap and the broad genetic heterogeneity of inherited peripheral neuropathies a comprehensive diagnostic genetic test is useful to establish the genetic cause in these clinical groups.
**Useful For:** Diagnosis of inherited peripheral neuropathies associated with known causal genes
Serving as a second-tier test for patients in whom previous targeted gene variant analyses for specific inherited peripheral neuropathy-related genes were negative. Identifying variants within genes known to be associated with inherited peripheral neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Peripheral Smear Interpretation, Whole Blood**

**Clinical Information:** Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count/special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.

**Useful For:** Detecting disease states or syndromes of the white blood cells, red blood cells, or platelet cell lines of a patient's peripheral blood

**Interpretation:** The laboratory will provide an interpretive report of percentage of white cells and, if appropriate, evaluation of white cells, red cells, and platelets.

**Reference Values:**
Only orderable as a reflex. For more information see SPSM / Morphology Evaluation (Special Smear), Blood.

**Clinical References:**

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**Pernicious Anemia Cascade, Serum**

**Clinical Information:** Vitamin B12 deficiency can be caused by many factors, one of which is pernicious anemia, a condition resulting in deficient production of intrinsic factor in the parietal cells of the stomach. Intrinsic factor is a protein that is needed to assist in the absorption of vitamin B12 into the small intestine. Vitamin B12 is converted into adenosylcobalamin, which converts L-methylmalonic acid to succinyl coenzyme A; hence, a decrease in vitamin B12 absorption in the intestine can cause an excess of methylmalonic acid within the body. Vitamin B12 deficiency may present with any...
combination of the following: macrocytic anemia, glossitis (painful inflammation of the tongue), peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients present with neurologic symptoms without macrocytic anemia. A group of tests is often required to establish the correct diagnosis as determination of vitamin B12 in serum does not detect all cases of vitamin B12 deficiency. Mayo Clinic's Department of Laboratory Medicine and Pathology offers a diagnostic algorithm to expedite the identification of patients with vitamin B12 deficiency. This algorithm takes into account the following facts: -The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for methylmalonic acid (MMA). -Nearly half of the cases of pernicious anemia can be unambiguously identified if the serum test for intrinsic factor blocking antibody is positive (this is a simpler and less expensive test than the MMA). -Serum gastrin is usually markedly increased in pernicious anemia (as a result of gastric atrophy) and this test can be used as a substitute for the more complicated and more expensive Schilling test of intestinal absorption of vitamin B12. The algorithm is similar to that published,(1) except that the serum gastrin assay is performed in place of the Schilling test. Experience with both Mayo Clinic and Mayo Clinic Laboratories' cases has corroborated that this is a cost-effective alternative to the Schilling test. In our experience, greater than 90% of laboratory test costs can be saved by using the algorithm rather than ordering all of the services for a patient suspected of having B12 deficiency. Furthermore, the substitution of the serum gastrin assay for the Schilling test offers 3 advantages: 1. It is an in vitro test that does not require administration of radioisotopes to patients 2. It can be performed on mailed-in specimens 3. It is much less expensive Only those tests that are appropriate, as defined by the algorithm, will be performed.

Useful For:

Diagnosis of pernicious anemia
Diagnosis of vitamin B12 deficiency-associated neuropathy

Interpretation:

Vitamin B12 >400 ng/L Results do not suggest B12 deficiency-no further testing.
Vitamin B12 150 to 400 ng/L Borderline vitamin B12 level-methylmalonic acid (MMA) is performed. If MMA is >0.40 nmol/mL, then intrinsic factor blocking antibody (IFBA) is performed. Vitamin B12 <150 ng/L Vitamin B12 deficiency-IFBA is performed. If IFBA is negative or indeterminate, then gastrin is performed. MMA < or =0.40 nmol/mL This value implies that there is no vitamin B12 deficiency at the cellular level. IFBA positive Consistent with pernicious anemia, Graves disease, or Hashimoto thyroiditis. Gastrin >200 pg/mL Result consistent with pernicious anemia. Gastrin <200 pg/mL Result does not suggest pernicious anemia. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:

180-914 ng/L

Clinical References:


Peroxisomal Disorder Gene Panel, Varies

Clinical Information:

Peroxisomes are responsible for catabolic actions of cells, including beta oxidation of very long-chain fatty acids, and anabolic actions, including biosynthesis of bile acids and plasmalogens. Peroxisomal disorders can be categorized into 2 major groups based on the function that is disrupted: peroxisomal biogenesis disorders and single peroxisomal enzyme deficiencies. Peroxisomal biogenesis disorders are caused by defective assembly of the organelle resulting in some amount of deficient functional peroxisomes. Severity of disease is dependent on amount of remaining functional peroxisomes. Peroxisomal biogenesis disorders include those in the Zellweger spectrum: Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Clinical features are usually progressive and include developmental delay, liver disease, blindness, and deafness. Severity is variable with Zellweger syndrome being the most severe and infantile Refsum disease being the least severe. These are due to variants in the PEX genes that are responsible for encoding proteins for peroxisome assembly. Peroxisomal enzyme deficiencies cause a disruption in peroxisomal function, although the
organelles remain intact. The most common peroxisomal disorder, X-linked adrenoleukodystrophy, is an enzyme deficiency due to variants in the ABCD1 gene. Other enzyme deficiencies include rhizomelic chondrodysplasia type 2 and 3, and congenital bile acid synthesis defect. This panel includes sequencing of 30 genes related to both peroxisomal biogenesis disorders and enzyme deficiencies.

**Useful For:** Follow up of abnormal biochemical result, usually very long-chain fatty acid test consistent with peroxisomal disorder Establishing a molecular diagnosis for patients with peroxisomal disorders Identifying variants within genes known to be associated with peroxisomal disorders, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**G160 605193**

**Peroxisomal Disorder Panel (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**PNZN 9789**

**Perphenazine, (Trilafon), Serum**

**Reference Values:**
Reference Range: 5.0 - 30.0 ng/mL
Low-dose therapeutic range for Perphenazine: 0.5 - 2.5 ng/mL

**PERS 82353**

**Persimmon, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to Persimmon, IgE Defining the allergen
responsible for eliciting signs and symptoms. Identifying allergens:
- Responsible for allergic disease
- and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**PMS2 65791 PGL_PMS2C (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**UPH24 606521 pH, 24 Hour, Urine**

**Clinical Information:** Urine pH is a measure of the acidity/alkalinity of urine and, by itself, usually provides little useful information. Under normal conditions its value is influenced by the type of diet. Some diets (eg, diets rich in meat) have more acid content than others (eg, vegetarian diets). Changes in urine pH may reflect systemic acid-base disorders. For example, the normal response during metabolic acidosis is a lowering of the urine pH to less than 5. If the pH is greater than 5, then a defect in urine acidification should be considered. A urine pH of greater than 8 is suggestive of infection by a urea-splitting organism such as Proteus mirabilis. Therapeutic interventions to either alkalinize or acidify the urine are necessary for some diseases. For example, some crystals have a propensity to form in alkaline urine, while others form in relative acidic urine, and changing the pH may reduce stone formation.

**Useful For:** Assessment of patients with metabolic acidosis, crystalluria, as well as monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis) using a 24-hour collection period

**Interpretation:** Dependent on clinical condition. A pH greater than 8 suggests the presence of urinary
tract infection with a urea-splitting organism.

**Reference Values:**
4.5-8.0

**Clinical References:**

**pH, Body Fluid**

**Clinical Information:** The pH value is a measure of hydrogen ion concentration. Increased metabolic activity and production of acidic byproducts (eg, lactic acid) due to infection is known to decrease pH. A variety of disease processes can alter pH values, therefore low pH has reduced specificity. Gastric content typically has a low pH, therefore measurement of pH has been used to help identify gastric fluid. Determining the pH value of a body fluid may help characterize the nature of the fluid.

**Useful For:** Indicating the presence of infections or fistulas. Verifying the effectiveness of treatment to reduce stomach pH. Diagnosing disease states characterized by abnormal stomach acidity. This test is not appropriate for measurement of pleural fluid pH as that measurement should be made using a blood gas analyzer locally due to sample stability and transport requirements.

**Interpretation:** Normal gastric fluid has a pH <3.0; any higher pH is abnormal. Low peritoneal fluid pH (<7.35) may be observed in spontaneous bacterial peritonitis.(1)

**Reference Values:** An interpretive report will be provided.

**pH, Fecal**

**Reference Values:**
5.0 - 8.5

**pH, Random, Urine**

**Clinical Information:** Urine pH is a measure of the acidity/alkalinity of urine and, by itself, usually provides little useful information. Under normal conditions its value is influenced by the type of diet (some diets: eg, diets rich in meat-having more acid content than others; eg, vegetarian diets). Assessment of urine pH may be useful in the evaluation of systemic acid-base disorder. For example, the normal response during metabolic acidosis is a lowering of the urine pH to less than 5. If it is greater than 5, then a defect in urine acidification should be considered. Often a urine pH above 8 is suggestive of infection of a urea splitting organism such as proteus mirabilis. Monitoring of urine pH may also be helpful during therapeutic interventions to either alkalinize the urine (such as for treatment of uric acid nephrolithiasis) or acidify the urine. Finally, when assessing crystalluria, noting the urine pH may be helpful since some crystals have a propensity to form in alkaline urine while others form in relative acidic urine.

**Useful For:** Assessment of patients with metabolic acidosis. Assessment of crystalluria. Monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis).
Interpretation: Dependent on clinical condition.

Reference Values:
4.5 to 8.0


**FPHAS**

**Phadiatop (Allergy Screen)**

Reference Values:
Negative

The Phadia Phadiatop test is an allergy screening test with excellent sensitivity and specificity for inhalant allergy. It uses an ImmunoCAP with a balanced mixture of representative allergens, including grasses, trees, weeds, cat, dog, mites and molds. A positive result indicates that the patient is allergic to one or more of these allergens; a negative indicates the patient is not allergic to inhalant allergens. Note that the test does not assess a patient’s sensitivity to food, drug, chemical or certain unusual or rare allergens.

**PHAGP**

**Phagocytic Primary Immunodeficiency (PID) Gene Panel, Varies**

Clinical Information: Primary immunodeficiencies (PID) that affect the function of phagocytes (neutrophils, monocytes, macrophages, and eosinophils) predispose patients to a narrow spectrum of specific infections as a result of impaired killing of bacteria and fungi. Chronic granulomatous disease (CGD), due to impaired production of reactive oxygen intermediates, is characterized by infections (ie, Staphylococcus aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia, and Aspergillus sp.) that involve the skin, lungs, lymph nodes, liver, and bones, although any organ or tissue can be affected. Patients may also experience immune dysregulation, resulting in granuloma formation, colitis, and other inflammatory disorders. While most affected individuals are diagnosed prior to 5 years of age, patients may present into late adulthood. Tests that measure neutrophil superoxide production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, including the dihydrorhodamine (DHR) or nitroblue tetrazolium (NBT) tests, may be used in establishing a diagnosis. X-linked CGD, the most common form, is caused by pathogenic variants in CYBB. In some cases, a contiguous gene deletion may result in CGD along with McLeod neuroacanthocytosis syndrome. In cases of a large contiguous gene deletion, patients may also inherit RPGR-related retinitis pigmentosa, Duchenne muscular dystrophy, and ornithine transcarbamylase deficiency. A chromosomal microarray may be indicated if a contiguous gene deletion is suspected. In addition to the X-linked form, CGD may also be inherited in an autosomal recessive pattern, due to biallelic pathogenic variants in the other genes that encode the remainder of the subunits of phagocyte NADPH (including CYBA, NCF1, NCF2, and NCF4 (Note: NCF1 is not currently included on this panel). Similarly to CGD, complete glucose 6-phosphate dehydrogenase (G6PD) deficiency can result in an increased susceptibility to infection due to impaired neutrophil respiratory burst. G6PD deficiency is also inherited in an X-linked pattern due to pathogenic variants in G6PD. Chronic nonspherocytic hemolytic anemia occurs in severe deficiency, while acute hemolytic episodes (typically triggered by some medications, ingestion of fava beans, viral or bacterial infections, etc) are observed in less severe G6PD deficiency. Patients with myeloperoxidase deficiency also show a reduced ability of the neutrophil to generate a respiratory burst, as evidenced by abnormal DHR results, but show normal superoxide production levels and NBT staining. Neutrophils contain azurophilic (or primary) granules, specific (or secondary) granules, and tertiary granules that contain antimicrobial substances. Azurophilic granules contain myeloperoxidase, bactericidal/permeability-increasing protein, defensins,
neutrophil elastase, and cathepsin G. Specific granules contain lactoferrin, lysozyme, NADPH oxidase, alkaline phosphatase, collagenase, histaminase, and cathelicidin. Tertiary granules contain cathepsin, gelatinase, and collagenase. Deficiency of myeloperoxidase can occur as an autosomal recessive condition due to variants in myeloperoxidase (MPO) and results in a susceptibility to Candida infections. 

Papillon-Lefèvre Syndrome (PALS) is an autosomal recessive disorder due to pathogenic variants in CTSC (lysosomal cysteine protease cathepsin C, also known as dipeptidyl peptidase I [DPP1]). DPP1 is necessary for posttranslational modification of the serine proteases in the neutrophil azurophilic granules, activation of granzymes A and B of cytotoxic lymphocytes, and activation of mast cell chymases. PALS typically presents with severe periodontal disease and keratosis palmoplantaris, along with mild immunodeficiency. In specific granule deficiency (SGD), neutrophils lack expression of secondary and tertiary granule proteins, have an atypical bilobed nuclear morphology, and demonstrate defects in chemotaxis and bactericidal activity. SGD is due to pathogenic variants in CEBPE, which is a myeloid-specific transcription factor. Leukocyte adhesion deficiencies (LAD) are characterized by recurrent bacterial infections due to reduced ability of neutrophils to adhere to various substances and migrate to sites of infection, as well as defective phagocytic and respiratory burst response to bacteria and yeast. Patients often are first noticed due to omphalitis, but later gingivitis/periodontitis, pneumonia, peritonitis, and deep abscesses may develop. LAD can be caused by pathogenic variants in ITGB2, which encodes for the CD18 antigen (LAD1); and SLC35C1, which encodes for a GDP-fucose transporter (LAD2) (Note: SLC35C1 is not currently included on this panel) or FERMT3 (LAD3). Although the neutrophil functional studies are similar between LAD1 and LAD2, the clinical course in LAD2 is milder, though patients may also present with other features (ie, mental and growth retardation) due to abnormal fucose metabolism. LAD3 presents similarly to LAD1, but platelets are also affected resulting in clotting defects. Pathogenic variants in RASGRP2 (also inherited in a recessive pattern) mimic the phenotype of LAD3. Recessively inherited defects in PMM2 (congenital disorder of glycosylation type IA) show diminished neutrophil chemotaxis resulting in severe infections. Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the formation of colonies of neutrophils and macrophages from bone marrow precursors, but is also required for proper neutrophil function. Recessive inheritance of pathogenic variants in CSF2RA, which encodes for the alpha chain of the GM-CSF receptor, disrupts GM-CSF signaling and results in defects in neutrophil adhesion, phagocytosis, superoxide formation, and microbial killing. Clinically, this manifests as pulmonary alveolar proteinosis and increased susceptibility to infections (pulmonary and extrapulmonary). The fMet-Leu-Phe receptor, encoded by FPR1, is located on the cell surface and is involved in chemotaxis phagocytic cells. Variants in FPR1 may present with aggressive periodontitis and FPR1 governs neutrophil function during acute inflammation. Netherton syndrome (NS), due to pathogenic variants in SPINK5 encoding LEKTI (lymphoepithelial Kazal-type-related inhibitor), is characterized by extensive skin inflammation, hair abnormalities, atopic manifestations, and recurrent bacterial infections. Although various immunologic defects have been suggested to contribute to the immune deficiency, in some cases NK cells demonstrate an immature phenotype with impaired degranulation and cytotoxic effects. Patients may also have decreased circulating B-cells and elevated IgE and IgA. Table1. Genes included in the Phagocytic / Chronic Granulomatous Disease PID Gene Panel

<table>
<thead>
<tr>
<th>GENE SYMBOL (ALIAS)</th>
<th>PROTEIN</th>
<th>OMIM</th>
<th>INHERITANCE</th>
</tr>
</thead>
</table>
| ITGB2               | Integrin beta-2 precursor 600065 AR Leukocyte adhesion deficiency type 1 MPO Myeloperoxidase precursor 606989 AR Myeloperoxidase deficiency NCF2 Neutrophil cytosol factor 2 isoform 1 608515 AR Chronic granulomatous disease NCF4 Neutrophil cytosol factor 4 isoform 2 601488 AR Chronic granulomatous disease PMM2 (CDG1) Phosphomannomutase 2 601785 AR Congenital disorder of glycosylation, type Ia RASGRP2 RAS guanyl-releasing protein 2 isoform a 605577 AR Bleeding disorder, platelet-type, 18, LAD-III SPINK5 Serine protease inhibitor Kazal-type 5 isoform b preproprotein 605010 AD/AR Atopy(AD), Netherton syndrome (AR) AD=autosomal dominant AR=autosomal recessive XL=X-linked

SGD is due to pathogenic variants in CEBPE, which is a myeloid-specific transcription factor. Leukocyte adhesion deficiencies (LAD) are characterized by recurrent bacterial infections due to reduced ability of neutrophils to adhere to various substances and migrate to sites of infection, as well as defective phagocytic and respiratory burst response to bacteria and yeast. Patients often are first noticed due to omphalitis, but later gingivitis/periodontitis, pneumonia, peritonitis, and deep abscesses may develop. LAD can be caused by pathogenic variants in ITGB2, which encodes for the CD18 antigen (LAD1); and SLC35C1, which encodes for a GDP-fucose transporter (LAD2) (Note: SLC35C1 is not currently included on this panel) or FERMT3 (LAD3). Although the neutrophil functional studies are similar between LAD1 and LAD2, the clinical course in LAD2 is milder, though patients may also present with other features (ie, mental and growth retardation) due to abnormal fucose metabolism. LAD3 presents similarly to LAD1, but platelets are also affected resulting in clotting defects. Pathogenic variants in RASGRP2 (also inherited in a recessive pattern) mimic the phenotype of LAD3. Recessively inherited defects in PMM2 (congenital disorder of glycosylation type IA) show diminished neutrophil chemotaxis resulting in severe infections. Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the formation of colonies of neutrophils and macrophages from bone marrow precursors, but is also required for proper neutrophil function. Recessive inheritance of pathogenic variants in CSF2RA, which encodes for the alpha chain of the GM-CSF receptor, disrupts GM-CSF signaling and results in defects in neutrophil adhesion, phagocytosis, superoxide formation, and microbial killing. Clinically, this manifests as pulmonary alveolar proteinosis and increased susceptibility to infections (pulmonary and extrapulmonary). The fMet-Leu-Phe receptor, encoded by FPR1, is located on the cell surface and is involved in chemotaxis phagocytic cells. Variants in FPR1 may present with aggressive periodontitis and FPR1 governs neutrophil function during acute inflammation. Netherton syndrome (NS), due to pathogenic variants in SPINK5 encoding LEKTI (lymphoepithelial Kazal-type-related inhibitor), is characterized by extensive skin inflammation, hair abnormalities, atopic manifestations, and recurrent bacterial infections. Although various immunologic defects have been suggested to contribute to the immune deficiency, in some cases NK cells demonstrate an immature phenotype with impaired degranulation and cytotoxic effects. Patients may also have decreased circulating B-cells and elevated IgE and IgA.
Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of primary immunodeficiency due to phagocytic defects, chronic granulomatous disease, or related disorders Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated primary immunodeficiency due to phagocytic defects, chronic granulomatous disease, or related disorders allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


Phencyclidine (PCP) Confirmation, Chain of Custody, Meconium

Clinical Information: Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles. (1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors. (1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects. (1,2) PCP is approximately 65% protein bound and has a volume of distribution (Vd) of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours. (2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can...
accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of phencyclidine in meconium is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

Negative

Positives are reported with a quantitative LC-MS/MS result.

Cutoff concentrations

PCP by LC-MS/MS: 10 ng/g

**Clinical References:**


Phencyclidine (PCP) Confirmation, Meconium

**Clinical Information:** Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles. PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors. PCP became a drug of abuse in the 1970s because of its hallucinogenic effects. PCP is approximately 65% protein bound and has a volume of distribution (Vd) of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours. Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.
evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Detection of in utero to phencyclidine (PCP) exposure up to 5 months before birth

**Interpretation:** The presence of phencyclidine (PCP) in meconium is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

**Negative**

Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations**

PCP by LC-MS/MS: 10 ng/g

**Clinical References:**


**Phencyclidine (PCP), Confirmation, serum**

**Reference Values:**

**Toxic:** Greater than 100 ng/mL

**Serious Toxicities likely:** Greater than 300 ng/mL

**Phencyclidine Confirmation, Chain of Custody, Random, Urine**

**Clinical Information:** Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotoninergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, yielding bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screening. PCP is excreted in the urine. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. This includes a record of the disposition of a specimen to document the personnel who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of drug abuse involving phencyclidine (street names: angel dust, hog, or angel hair) in urine specimens handled through the chain-of-custody process

**Interpretation:** The presence of phencyclidine (PCP) in urine is a strong indicator that the patient has used PCP.

**Reference Values:**

**Negative**

**Cutoff concentrations**

**IMMUNOASSAY SCREEN**

<25 ng/mL
PHENCYCLIDINE BY GC-MS
<10 ng/mL


**Phencyclidine Confirmation, Random, Urine**

**Clinical Information:** Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotoninergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, yielding bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screening. PCP is excreted in the urine.

**Useful For:** Detection of drug abuse involving phencyclidine (street names: angel dust, hog, or angel hair)

**Interpretation:** The presence of phencyclidine (PCP) in urine is a strong indicator that the patient has used PCP.

**Reference Values:**
Negative
Cutoff concentrations
Phencyclidine by GC-MS: <10 ng/mL


**Phenobarbital, Serum**

**Clinical Information:** Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations above 40.0 mcg/mL. Symptoms become severe at concentrations of 60.0 mcg/mL and higher. Toxicity becomes life-threatening at concentrations over 100.0 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

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Useful For: Monitoring for appropriate therapeutic concentration of phenobarbital Assessing compliance or toxicity

Interpretation: Clinical response to the drug correlates strongly with blood concentration. Dosage adjustments are made after 2 weeks of therapy to achieve steady-state blood levels in the range of 20.0 to 40.0 mcg/mL for adults; 15.0 to 30.0 mcg/mL for infants and children. Patients chronically administered phenobarbital usually do not experience sedation unless the blood concentration is above 40.0 mcg/mL.

Reference Values:
Therapeutic: 10.0-40.0 mcg/mL
Critical value: > or =60.0 mcg/mL


FPGT 91757 Phenosense Combination HIV Drug Resistance Assay
Reference Values:
A final report will be attached in MayoAccess.

FPFUZ 91755 Phenosense Entry HIV Drug Resistance Assay
Reference Values:
A final report will be attached in MayoAccess.

FPHIV 91756 Phenosense HIV Drug Resistance Replication Capacity
Reference Values:
A final report will be attached in MayoAccess.

PKUBS 65593 Phenylalanine and Tyrosine, Blood Spot
Clinical Information: Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of not only PAH, but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia; guanosine triphosphate cyclodrolase deficiency, 6-priuvoyl tetrahydropterine synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and mental retardation though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that is derived from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia
can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

**Useful For:** Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia. This test is not sufficient for follow-up for abnormal newborn screening results or for establishing a diagnosis of a specific cause of hyperphenylalaninemia.

**Interpretation:** The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

**Reference Values:**

**PHENYLALANINE**

27.0-107.0 nmol/mL

**TYROSINE**

<4 weeks: 40.0-280.0 nmol/mL

≥4 weeks: 25.0-150.0 nmol/mL

**Clinical References:**


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**Phenylalanine and Tyrosine, Plasma**

**Clinical Information:** Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of not only PAH, but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia: guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterine synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and mental retardation though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that derives from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

**Useful For:** Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia.

**Interpretation:** The quantitative results of phenylalanine and tyrosine with age-dependent reference...
values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

**Reference Values:**

**PHENYLALANINE**

- Premature: 98-213 nmol/mL
- 0-31 days: 38-137 nmol/mL
- 1-24 months: 31-75 nmol/mL
- 2-18 years: 26-91 nmol/mL
- > or =19 years: 35-85 nmol/mL

Conversion Formulas:

- Result in mg/dL x 60.5 = result in nmol/mL
- Result in nmol/mL x 0.0165 = result in mg/dL

**TYROSINE**

- Premature: 147-420 nmol/mL
- 0-31 days: 55-147 nmol/mL
- 1-24 months: 22-108 nmol/mL
- 2-18 years: 24-115 nmol/mL
- > or =19 years: 34-112 nmol/mL

Conversion Formulas:

- Result in mg/dL x 55.2 = result in nmol/mL
- Result in nmol/mL x 0.0181 = result in mg/dL

**Clinical References:**


**Clinical Information:**

Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (occurring in about 1:10,000-1:15,000 births) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of not only PAH, but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia; guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterine synthase deficiency.
Dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and mental retardation though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that is derived from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

**Useful For:** Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia. This test is not sufficient for follow-up for abnormal newborn screening results or for establishing a diagnosis of a specific cause of hyperphenylalaninemia.

**Interpretation:** The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

**Reference Values:**
- **PHENYLALANINE:**
  - 27.0-107.0 nmol/mL
- **TYROSINE**
  - <4 weeks: 40.0-280.0 nmol/mL
  - > or =4 weeks: 25.0-150.0 nmol/mL

**Clinical References:**
L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Recently, variants in DNAJC12, which encodes a heat-shock protein that interacts with the phenylalanine, tyrosine, and tryptophan hydroxylases to help catalyze the conversion of the substrates to their respective products, has been shown to cause hyperphenylalaninemia, progressive neurodegeneration, and dystonia. Treatment may include early administration of BH4 and/or neurotransmitter precursors. Related additional disorders of neurotransmitter metabolism include: - Aromatic l-amino acid decarboxylase (AADC) deficiency, caused by variants in DDC, is an autosomal recessive inborn error in neurotransmitter metabolism that leads to combined serotonin and catecholamine deficiency. - Patients with dopa-responsive dystonia due to variants in SPR causing sepiapterin reductase deficiency have progressive psychomotor retardation and dystonia. - Variants in tyrosine hydroxylase (TH) prevent the conversion of L-tyrosine to L-dopa resulting in Segawa syndrome. - Variants in SLC18A2, a vesicular transporter of dopamine, cause infantile parkinsonism-dystonia-2 (PKDYS2)

**Useful For:** Follow up for abnormal biochemical results suggestive of a phenylalanine disorder. Establishing a molecular diagnosis for patients with phenylalanine disorders. Identifying variants within genes known to be associated with phenylalanine disorders, allowing for predictive testing of at-risk family members.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**Phenytoin, Free, Serum**

**Clinical Information:** Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Phenytoin is highly protein-bound (90%), mostly to albumin. Ten percent of the phenytoin circulates in the free, unbound form. Free phenytoin is the active form of the drug, available to cross biologic membranes and bind to receptors. Increased free phenytoin produces an enhanced pharmacologic effect. At the same time, the free fraction is more available to the liver to be metabolized, so it is cleared more quickly. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood
concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma.

Useful For: Monitoring for appropriate therapeutic concentration of free phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure Assessing compliance and toxicity

Interpretation: Dose should be adjusted to achieve steady-state blood concentration of free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. Severe toxicity occurs when the free phenytoin concentration is > or =2.5 mcg/mL. However, response and side effects will be individual.

Reference Values:
Therapeutic: 1.0-2.0 mcg/mL Critical value: > or =2.5 mcg/mL


Phenytoin, Total and Free, Serum

Clinical Information: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. Phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

Useful For: Monitoring for appropriate therapeutic concentration of both free and total phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure

Interpretation: Dose should be adjusted to achieve steady-state concentrations of total phenytoin
between 10.0 and 20.0 mcg/mL, and free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. However, response and side effects will be individual. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

**Reference Values:**

**Phenytoin, Total**
- **Therapeutic:** 10.0-20.0 mcg/mL
- **Critical value:** > or =30.0 mcg/mL

**Phenytoin, Free**
- **Therapeutic:** 1.0-2.0 mcg/mL
- **Critical value:** > or =2.5 mcg/mL

**Clinical References:**

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**Phenytoin, Total and Phenobarbital Group, Serum**

**Clinical Information:** Phenytoin, Total: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin which causes an increase in the free fraction. Valproic acid, an antiepileptic frequently coadministered with phenytoin, competes for the same binding sites on albumin as phenytoin. Valproic acid displaces phenytoin from albumin, reducing the bound fraction and increasing the free fraction. The overall effect of coadministration of a therapeutic dose of valproic acid is that the total concentration of phenytoin decreases due to increased clearance but the free fraction increases; the free concentration of phenytoin, which is the active form remains virtually the same. Thus, no dosage adjustment is needed when valproic acid is added to maintain the same pharmacologic effect, but the total concentration of phenytoin decreases. In contrast to the valproic acid situation, in renal failure, there is not the same opportunity for the free phenytoin fraction to be cleared. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. The free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is >30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative. Phenobarbital: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial
seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations >40 mcg/mL. Symptoms become severe at concentrations > or =60 mcg/mL. Toxicity becomes life-threatening at concentrations >100 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

**Useful For:** Monitoring for appropriate therapeutic concentration of phenytoin and phenobarbital

**Assessing compliance or toxicity**

**Interpretation:** The therapeutic ranges for adults taking phenytoin have been established at 10 to 20 mcg/mL for total phenytoin (bound plus unbound). The therapeutic range for phenobarbital is 10 to 40 mcg/mL. Within these ranges, most people will respond to the drugs without symptoms of toxicity. However, response and side effects will be individual. Dosage determinations and adjustments must be evaluated on a case-by-case basis. A free (unbound) phenytoin level may also need to be ordered when a person has kidney failure, liver disease, hypoalbuminemia, or is taking other medications like aspirin, naproxen, or ibuprofen, in which situation the percentage of free (active) phenytoin may be increased.

**Reference Values:**

**PHENYTOIN, TOTAL**

- Therapeutic: 10.0-20.0 mcg/mL
- Critical value: > or =30.0 mcg/mL

**PHENOBARBITAL**

- Therapeutic: 10.0-40.0 mcg/mL:
- Critical value: > or =60.0 mcg/mL

**Clinical References:**

frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy in renal failure. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is above 30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

**Useful For:** Monitoring for appropriate therapeutic concentration Assessing compliance or toxicity

**Interpretation:** Dose should be adjusted to achieve steady-state total phenytoin concentrations between 10.0 and 20.0 mcg/mL. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

**Reference Values:**
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

**Clinical References:**

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**Phoma betae, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Phoma betae Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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**Current as of June 14, 2021 12:13 pm CDT**
800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FFPET 75559**

**Phosphatidylethanol (PEth), whole blood**

**Reference Values:**

Reference range: NEGATIVE

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**PSPT 64704**

**Phosphatidylserine/Prothrombin Antibody, IgG and IgM, Serum**

**Clinical Information:** According to the 2006 revised Sapporo classification criteria, a diagnosis of antiphospholipid syndrome (APS) is based on the presence of specific pregnancy-related morbidities, arterial or venous thrombosis in association with persistent lupus anticoagulant (LAC), anticardiolipin IgG/IgM or anti-beta 2-glycoprotein I IgG/IgM antibodies.(1) Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. LAC is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation.(2) Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected in solid-phases immunoassays using beta 2-glycoprotein I-dependent cardiolipin/or beta 2-glycoprotein I alone as substrate, respectively.(2,3) There is evidence from multiple studies to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT).(4-9) Like beta 2-glycoprotein-dependent I cardiolipin, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. In a systematic review, Sciascia et al demonstrated that the presence of anti-PS/PT IgG antibodies is an independent risk factor for arterial and/or venous thrombotic events, with odds ratio (OR) of 5.11 (95% CI: 4.2-6.3).(4) A multicenter study showed that IgG anti-PS/PT were more prevalent in APS patients (51%) than in those without (9%), OR 10.8, 95% CI (4.0-29.3), p <0.0001.(5) Furthermore, a number of studies have shown clinical and laboratory evidence that PS/PT antibodies may be a useful second-line test for the evaluation of patients at-risk or suspected with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LAC testing.(6,7) While anti-PS/PT antibodies were highly prevalent and correlated with other anti-PL antibodies, IgG anti-PS/PT conferred a high risk for thrombosis (8,9) but not for pure hematologic involvement.(9) These antibodies may also be seen in patients with other autoimmune diseases such as...
systemic lupus erythematosus. In individuals who test positive for antiphospholipid antibodies without clinical features of APS (carriers), the cumulative incidence rate of thrombotic events has also been reported to be significantly higher for anti-PS/PT IgG positive than anti-PS/PT IgM positive subjects.

**Useful For:** Preferred second-tier panel for the detection of IgG and IgM antibodies against phosphatidylserine/prothrombin complex in patients with strong suspicion of antiphospholipid syndrome (APS) who are negative for the APS criteria laboratory tests (lupus anticoagulant, IgG and IgM anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibodies). May be useful for the evaluation of patients with prior positive lupus anticoagulant results who are on direct oral anticoagulant (DOAC) therapy. May be useful as a risk marker for thrombosis in antiphospholipid antibody carriers.

**Interpretation:** A positive and persistent result for anti-phosphatidylserine/prothrombin complex IgG and/or IgM antibodies may be suggestive of a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial, venous, or specific pregnancy-related morbidities. These antibodies may also exist prior to the occurrence APS clinical manifestations as well as in patients with other systemic autoimmune diseases such as systemic lupus erythematosus (SLE). Anti-phosphatidylserine/prothrombin complex IgG antibodies have relatively higher correlations with positive results for lupus anticoagulant than the IgM isotype as well as significant risk for APS-associated thrombotic events compared to the IgM isotype in antiphospholipid antibody carriers. A negative result does not exclude the diagnosis of APS, as other phospholipid/protein antibodies are also associated with this disorder.

**Reference Values:**
- Negative < =30.0 U
- Borderline 30.1-40.0 U
- Positive > =40.1 U

**Clinical References:**
Clinical Information: According to the 2006 revised Sapporo classification criteria, a diagnosis of antiphospholipid syndrome (APS) is based on the presence of specific pregnancy-related morbidities, arterial or venous thrombosis in association with persistent lupus anticoagulant (LAC), anti-cardiolipin IgG/IgM or anti-beta 2-glycoprotein I IgG/IgM antibodies.(1) Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. LAC is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation.(2) Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected in solid-phases immunoassays using beta 2-glycoprotein I-dependent cardiolipin/or beta 2-glycoprotein I alone as substrate, respectively.(2,3) There is evidence from multiple studies to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT).(4-9) Like beta 2-glycoprotein-dependent I cardiolipin, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. In a systematic review, Sciascia et al demonstrated that the presence of anti-PS/PT IgG antibodies is an independent risk factor for arterial and/or venous thrombotic events, with odds ratio (OR) of 5.11 (95% CI: 4.2-6.3).(4) A multicenter study showed that IgG anti-PS/PT were more prevalent in APS patients (51%) than in those without (9%), OR 10.8, 95% CI (4.0-29.3), p <0.0001.(5) Furthermore, a number of studies have shown clinical and laboratory evidence that PS/PT antibodies may be a useful second-line test for the evaluation of patients at-risk or suspected with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LAC testing.(6,7) While anti-PS/PT antibodies were highly prevalent and correlated with other anti-PL antibodies, IgG anti-PS/PT conferred a high risk for thrombosis (8,9) but not for pure hematologic involvement.(9) These antibodies may also be seen in patients with other autoimmune diseases such as systemic lupus erythematosus.(5,8) In individuals who test positive for antiphospholipid antibodies without clinical features of APS (carriers), the cumulative incidence rate of thrombotic events has also been reported to be significantly higher for anti-PS/PT IgG positive than anti-PS/PT IgM positive subjects.(10)

Useful For: Detection of IgG antibodies against phosphatidylserine/prothrombin complex in patients with strong suspicion of antiphospholipid syndrome (APS) who are negative for the APS criteria laboratory tests (lupus anticoagulant, IgG and IgM anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibodies) May be useful for the evaluation of patients with prior positive lupus anticoagulant results who are on direct oral anticoagulant (DOAC) therapy May be useful as a risk marker for thrombosis in antiphospholipid antibody carriers

Interpretation: A positive and persistent result for anti-phosphatidylserine/prothrombin complex IgG antibodies may be suggestive of a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial, venous, or specific pregnancy-related morbidities. These antibodies may also exist prior to the occurrence APS clinical manifestations as well as in patients with other systemic autoimmune diseases such systemic lupus erythematosus (SLE). Anti-phosphatidylserine/prothrombin complex IgG antibodies have relatively higher correlations with positive results for lupus anticoagulant than the IgM isotype as well as significant risk for APS-associated thrombotic events compared to the IgM isotype in antiphospholipid antibody carriers. A negative result does not exclude a diagnosis of APS, as other phospholipid and/or protein antibodies are also associated with this disorder.

Reference Values: Negative < or =30.0 U Borderline 30.1-40.0 U Positive > or =40.1 U


Clinical Information: According to the 2006 revised Sapporo classification criteria, a diagnosis of antiphospholipid syndrome (APS) is based on the presence of specific pregnancy-related morbidities, arterial or venous thrombosis in association with persistent lupus anticoagulant (LAC), anticardiolipin IgG/IgM or anti-beta 2-glycoprotein I IgG/IgM antibodies. Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. LAC is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation. Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected in solid-phases immunoassays using beta 2-glycoprotein I-dependent cardiolipin/or beta 2-glycoprotein I alone as substrate, respectively. There is evidence from multiple studies to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT). Like beta 2-glycoprotein-dependent I cardiolipin, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. In a systematic review, Sciascia et al demonstrated that the presence of anti-PS/PT IgG antibodies is an independent risk factor for arterial and/or venous thrombotic events, with odds ratio (OR) of 5.11 (95% CI: 4.2-6.3). A multicenter study showed that IgG anti-PS/PT were more prevalent in APS patients (51%) than in those without (9%), OR 10.8, 95% CI (4.0-29.3), p <0.0001. Furthermore, a number of studies have shown clinical and laboratory evidence that PS/PT antibodies may be a useful second-line test for the evaluation of patients at-risk or suspected with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LAC testing. While anti-PS/PT antibodies were highly prevalent and correlated with other anti-PL antibodies, IgG anti-PS/PT conferred a high risk for thrombosis (8,9) but not for pure hematologic involvement. These antibodies may also be seen in patients with other autoimmune diseases such as systemic lupus erythematosus. In individuals who test positive for antiphospholipid antibodies without clinical features of APS (carriers), the cumulative incidence rate of thrombotic events has also been reported to be significantly higher for anti-PS/PT IgG positive than anti-PS/PT IgM positive subjects.

Useful For: Detection of IgM antibodies against phosphatidylserine/prothrombin complex in patients with strong suspicion of antiphospholipid syndrome (APS) who are negative for the APS criteria laboratory tests (lupus anticoagulant, IgG and IgM anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibodies) May be useful for the evaluation of patients with prior positive lupus anticoagulant results who are on direct oral anticoagulant (DOAC) therapy May be useful as a risk marker for thrombosis in antiphospholipid antibody carriers

Interpretation: A positive and persistent result for anti-phosphatidylserine/prothrombin complex IgM antibodies may be suggestive of a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial, venous or specific pregnancy-related morbidities. These antibodies may also exist.
prior to the occurrence APS clinical manifestations as well as in patients with other systemic autoimmune diseases such systemic lupus erythematosus (SLE). A negative result does not exclude a diagnosis of APS, as other phospholipid or protein antibodies are also associated with this disorder.

**Reference Values:**
- Negative ≤ 30.0 U
- Borderline 30.1-40.0 U
- Positive > or =40.1 U

**Clinical References:**

**Phosphofructokinase Enzyme Activity, Blood**

**Clinical Information:** Phosphofructokinase (PFK) is the third enzyme in glycolysis. It converts fructose-6-phosphate to fructose 1,6-diphosphate. PFK deficiency, also called glycogen storage disease, type VII or Tarui disease (OMIM 232800), is a rare hereditary autosomal recessive disorder that is typically noticed in childhood. Different clinical subtypes (classical, late-onset, infantile and hemolytic) have been described. Manifestations can vary including exercise intolerance, exertional myopathy, nausea, stiffness, and myoglobinuria. Although not classically described, a second-wind effect is noticed by some patients (1). A subset of individuals have compensated (high normal hemoglobin values) or mild hemolytic anemia, episodic jaundice, hyperuricemia, or gout-like symptoms. No distinctive morphologic abnormalities are seen on the peripheral blood smear. Red blood cell PFK activity is typically partially decreased (30-50% mean normal) and muscle biopsy PFK activity is markedly decreased.

**Useful For:**
- Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia
- Evaluation of individuals with exercise intolerance or myopathy
- Genetic studies in families with phosphofructokinase deficiency

**Interpretation:** Clinically significant disorders due to phosphofructokinase (PFK) deficiency are associated with red blood cell activity levels less than 50% of mean normal. Unaffected heterozygotes
have been reported with levels of 63% of normal. Therefore genetic correlation will often be important in ambiguous cases.

Reference Values:
> or =12 months of age: 5.8-10.9 U/g Hb
Reference values have not been established for patients who are <12 months of age.


Phosphofructokinase Enzyme Activity, Blood

Clinical Information: Phosphofructokinase (PFK) is the third enzyme in glycolysis. It converts fructose 6-phosphate to fructose 1,6-diphosphate. PFK deficiency, also called glycogen storage disease, type VII or Tarui disease (OMIM 232800), is a rare hereditary autosomal recessive disorder that is typically noticed in childhood. Different clinical subtypes: classical, late-onset, infantile and hemolytic, have been described. Manifestations can vary and include exercise intolerance, exertional myopathy, nausea, stiffness, and myoglobinuria. Although not classically described, a second-wind effect is noticed by some patients. (1) A subset of individuals has compensated (high normal hemoglobin values) or mild hemolytic anemia, episodic jaundice, hyperuricemia, or gout-like symptoms. No distinct morphologic abnormalities are seen on the peripheral blood smear. Red blood cell PFK activity is typically partially decreased (30-50% mean normal) and muscle biopsy PFK activity is markedly decreased.

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia Evaluation of individuals with exercise intolerance or myopathy Genetic studies in families with phosphofructokinase deficiency

Interpretation: Clinically significant disorders due to phosphofructokinase (PFK) deficiency are associated with red blood cell activity levels less than 50% of mean normal. Unaffected heterozygotes have been reported with levels of 63% of normal. Therefore genetic correlation will often be important in ambiguous cases.

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 5.8-10.9 U/g Hb
Reference values have not been established for patients who are less than 12 months of age.

features and new molecular findings in muscle phosphofructokinase deficiency (GSD type VII).


**Phosphoglycerate Kinase Enzyme Activity, Blood**

**Clinical Information:** Phosphoglycerate kinase (PGK) is an enzyme that converts 1,3-diphosphoglycerate (1,3-DPG) to 3-phosphoglyceric acid (3-PGA) in one of the adenosine triphosphate (ATP) generating steps in glycolysis. PGK deficiency (OMIM # 300653) is an X-linked disorder with a variable clinical phenotype. Manifestations include hemolytic anemia, myopathy/rhabdomyolysis, or neurologic impairment. Patients can have 1 or 2 systems affected but rarely have all 3. Clinical severity may not correlate with enzyme activity and female heterozygotes may possibly be mildly affected.

**Useful For:** Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia, especially if X-linked inheritance pattern. Evaluation of individuals with myopathic or neurologic symptoms

**Interpretation:** In phosphoglycerate kinase (PGK) deficiency, red blood cell activity levels have been reported ranging from 1% to 49% of mean normal; however, affected patients more typically have values less than 20% of normal mean.(1)

**Reference Values:** Only available as part of a profile. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation
- EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation

> or =12 months: 142-232 U/g Hb

Reference values have not been established for patients who are less than 12 months of age.


**Phosphoglycerate Kinase Enzyme Activity, Blood**

**Clinical Information:** Phosphoglycerate kinase (PGK) is an enzyme that converts 1,3-diphosphoglycerate (1,3-DPG) to 3-phosphoglyceric acid (3-PGA) in one of the adenosine triphosphate (ATP) generating steps in glycolysis. PGK deficiency (OMIM # 300653) is an X-linked disorder with a variable clinical phenotype. Manifestations include hemolytic anemia, myopathy/rhabdomyolysis, or neurologic impairment. Patients can have 1 or 2 systems affected, but rarely have all 3. Clinical severity may not correlate with enzyme activity, and female heterozygotes may possibly be mildly affected.

**Useful For:** Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia, especially if X-linked inheritance pattern. Evaluation of individuals with myopathic or neurologic symptoms.
**Interpretation:** In phosphoglycerate kinase (PGK) deficiency, RBC activity levels have been reported ranging from 1% to 49% of mean normal; however, affected patients more typically have values below 20% of normal mean. (1)

**Reference Values:**
> or =12 months: 142-232 U/g Hb

Reference values have not been established for patients who are less than 12 months of age.

**Clinical References:**

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**Phospholipase A2 Receptor (PLA2R), Renal Biopsy**

**Clinical Information:** Membranous nephropathy is the most common cause of nephrotic syndrome in white adults. Eighty-five percent of membranous nephropathy cases are primary or idiopathic and the other 15% are secondary. Phospholipase A2 receptor (PLA2R) is an antigen located on podocytes. The majority of cases of primary membranous nephropathy have circulating autoantibodies against PLA2R.

**Useful For:** Distinguishing primary membranous nephropathy from secondary membranous nephropathy

**Interpretation:** This test, (when not accompanied by a pathology consultation request) will be reported as either positive or negative.

**Clinical References:**

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**Phospholipase A2 Receptor Antibodies, Serum**

**Clinical Information:** Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type phospholipase A2 receptor (PLA2R). (1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression. (2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease (CKD) awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation. (2)

**Useful For:** Distinguishing primary from secondary membranous nephropathy

**Interpretation:** Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor
(PLA2R) antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

**Reference Values:**

**ELISA:**
- Negative: <14 RU/mL
- Borderline: > or =14-<20 RU/mL
- Positive: > or =20 RU/mL

**IFA:** Negative

**Clinical References:**

**PA2RE 603600**

**Phospholipase A2 Receptor Enzyme-Linked Immunosorbent Assay, Serum**

**Clinical Information:** Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease (CKD) awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation.(2) A Mayo Clinic Renal Lab data suggest that there is a high concordance between the enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay PLA2R results; however, the ELISA assay alone may be preferred for monitoring patients with membranous nephropathy over time for trends in anti-PLA2R antibody levels.

**Useful For:** Distinguishing primary from secondary membranous nephropathy. Monitoring patients with membranous nephropathy, over time, for trends in anti-PLA2R antibody levels

**Interpretation:** Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor (PLA2R) antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

**Reference Values:**
- Negative: <14 RU/mL
- Borderline: > or =14-19 RU/mL
- Positive: > 19 RU/mL

**Clinical References:**

**PA2RI 603601**

**Phospholipase A2 Receptor Indirect Immunofluorescence Assay, Serum**

**Clinical Information:** Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier,
resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary
MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type
phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R
antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome
if a biopsy is not possible. Among patients with chronic kidney disease (CKD) awaiting kidney
transplantation, higher levels of anti-PLA2R could predict those more likely to recur after
transplantation.(2) Mayo Clinic Renal Lab data suggest that there is a high-concordance between the
enzyme-linked immunosorbent assay and indirect immunofluorescence assay (IFA) PLA2R results,
although the IFA may be more sensitive in monitoring patients with membranous nephropathy with
very low antibody titres.

Useful For: Distinguishing primary from secondary membranous nephropathy Screening for
anti-PLA2R antibodies Monitoring patients with membranous nephropathy at very low antibody titres

Interpretation: According to the manufacturer’s package insert, the EUROIMMUN Anti-PLA2R
indirect immunofluorescence assay (IFA) was positive in 77.1% of patients with biopsy proven primary
membranous nephropathy (pMN). This corresponds well with published literature that approximately
70% of patients with pMN will have anti-PLA2R antibodies.

Reference Values:
Negative

Hornig N, Lange S, et al: Differential diagnosis of membranous nephropathy with autoantibodies to
phospholipase A2 receptor 1. Autoimmun Rev 2014 Feb;13(2)108-113

EURO
64328
Phospholipase A2 Receptor, Enzyme Linked Immunosorbent
Assay, Serum
Reference Values:
For more information see PLA2R / Phospholipase A2 Receptor Antibodies, Serum.

SCOPE
64326
Phospholipase A2 Receptor, Indirect Immunofluorescence
Assay, Serum
Reference Values:
For more information see PLA2R / Phospholipase A2 Receptor Antibodies, Serum.

ACLIP
86179
Phospholipid (Cardiolipin) Antibodies, IgA, Serum
Clinical Information: The plasma membranes of mammalian cells are formed from phospholipids.
Anionic phospholipids (eg, phosphatidylserine) are found on the cytoplasmic surface and neutral
phospholipids (eg, phosphatidylcholine) predominate on the external surface. Membrane phospholipids
participate in several important cellular functions including exchanging metabolites across membranes,
transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes.(1)
Cellular activation is often accompanied by the translocation of anionic phospholipids to the external
membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is
translocated from the inner platelet membrane and provides a surface for the assembly of the
prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively
charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural
autoantibodies.(2) Plasma from normal individuals contains low concentrations of natural IgG
autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and
increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies
when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2-glycoprotein 1 (beta-2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 GP1. Beta-2 GP1 is a 326-amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM anti-beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anticardiolipin and anti-beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgA antibodies

Interpretation: APL, GPL and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype (APL) may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA phospholipid (cardiolipin) antibody results greater than 15 APL with negative IgG and IgM phospholipid (cardiolipin) antibody results are not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

Reference Values:
<15.0 APL (negative)
15.0-39.9 APL (weakly positive)
40.0-79.9 APL (positive)
> or =80.0 APL (strongly positive)

APL refers to IgA Phospholipid Units. One APL unit is 1 microgram of IgA antibody.
Reference values apply to all ages.

Phospholipid (Cardiolipin) Antibodies, IgG and IgM, Serum

Clinical Information: The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (e.g., phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (e.g., phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2 glycoprotein 1 and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 glycoprotein 1(beta-2 GP1beta-2 GP1). Beta-2 GP1 is a 326 amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro. Not all phospholipid antibodies possess lupus anticoagulant activity.

Useful For: Testing for phospholipid antibodies is indicated in the following clinical situations:
- Unexplained arterial or venous thrombosis
- A history of pregnancy morbidity defined as 1 or more unexplained arterial or venous thrombosis -A history of pregnancy morbidity defined as 1 or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, 1 or more premature births before 34 weeks of gestation caused by severe preeclampsia or placental insufficiency, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation with no identifiable maternal hormonal or anatomic, or maternal or paternal chromosomal causes -Presence of an unexplained cutaneous circulatory disturbance, eg, livido reticularis or pyoderma gangrenosum -Presence of a systemic rheumatic disease especially lupus erythematosus -Unexplained thrombocytopenia or hemolytic anemia -Possible nonbacterial, thrombotic endocarditis
**Interpretation:** Positive and strongly positive results for phospholipid antibodies (> or =40 GPL and/or MPL) are a diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of phospholipid antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Detection of phospholipid antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <15.0 MPL or GPL (negative)
- 15.0-39.9 MPL or GPL (weakly positive)
- 40.0-79.9 MPL or GPL (positive)
- > or =80.0 MPL or GPL (strongly positive)

MPL refers to IgM Phospholipid Units. One MPL unit is 1 microgram of IgM antibody.

GPL refers to IgG Phospholipid Units. One GPL unit is 1 microgram of IgG antibody.

Reference values apply to all ages.

**Clinical References:**

**Phospholipid (Cardiolipin) Antibodies, IgG, Serum**

**Clinical Information:** The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (eg, phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (eg, phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes.(1) Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies.(2) Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta-2 glycoprotein 1 (beta-2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 GP1. Beta-2 GP1 is a 326-amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity.(3) Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules
can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met.(4) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM anti-beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anticardiolipin and beta GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.(4)

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgG antibodies

Interpretation: APL, GPL, and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. An IgA phospholipids (cardiolipin) antibody result above 15 APL with negative IgG and IgM phospholipids (cardiolipin) antibody results is not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

Reference Values:

<15.0 GPL (negative)
15.0-39.9 GPL (weakly positive)
40.0-79.9 GPL (positive)
> or =80.0 GPL (strongly positive)

GPL refers to IgG Phospholipid Units. One GPL unit is 1 microgram of IgG antibody.
Reference values apply to all ages.


Phospholipid (Cardiolipin) Antibodies, IgM, Serum

Clinical Information: The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (eg, phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (eg, phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes,
transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. (1) Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. (2) Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta-2 glycoprotein 1 (beta-2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 GP1. Beta-2 GP1 is a 326-amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. (3) Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. (4) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM anti-beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anticardiolipin and anti-beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity. (4)

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgM antibodies

**Interpretation:** APL, GPL, and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. An IgA phospholipid (cardiolipin) antibody result above 15 APL with negative IgG and IgM phospholipids (cardiolipin) antibody results is not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

**Reference Values:**

- <15.0 MPL (negative)
- 15.0-39.9 MPL (weakly positive)
- 40.0-79.9 MPL (positive)
- > or =80.0 MPL (strongly positive)
MPL refers to IgM Phospholipid Units. One MPL unit is 1 microgram of IgM antibody. Reference values apply to all ages.

**Clinical References:**

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**PMMIL**

**Phosphomannomutase and Phosphomannose Isomerase, Leukocytes**

**Clinical Information:** Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of inherited metabolic diseases that affect one of the steps of the pathway involved in glycosylation. CDG typically present as multisystemic disorders and may include developmental delay, hypotonia, abnormal magnetic resonance imaging (MRI) findings, hypoglycemia, and protein-losing enteropathy. There is considerable variation in the severity of this group of diseases, which can range from hydrops fetalis to a mild presentation in adults. In some subtypes (Ib, in particular) intelligence is not compromised. Phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of the enzyme phosphomannomutase-2, encoded by the PMM2 gene. It is the most common CDG worldwide. Patients with CDG-Ia have moderate to severe neurological disease, more or less typical dysmorphology, and variable involvement of other organ systems. Severely affected individuals with CDG-Ia usually present in the neonatal period with failure to thrive, developmental delay, abnormal subcutaneous fat distribution, elevated liver transaminases, and abnormal MRI findings. Later presenting individuals can have clinical features that include ataxia, significantly delayed motor and language development, seizures, stroke-like episodes, retinitis pigmentosa, joint contractures and skeletal deformities. An adult form has also been described. Currently, there is no cure and treatment remains primarily supportive and symptomatic. Phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of phosphomannose isomerase, an enzyme encoded by the MPI gene. This CDG subtype is unique in that there is little to no involvement of the central nervous system. It is mainly hepatic-intestinal without dysmorphology, and the primary clinical manifestations are a result of aberrant gastrointestinal function. In particular, individuals with CDG-Ib may present with failure to thrive, hypoglycemia, chronic diarrhea, and protein-losing enteropathy. CDG-Ib is also unique in that it can be effectively treated with mannose supplementation, though can be fatal if left untreated.

**Useful For:** Diagnosing congenital disorders of glycosylation Ia (phosphomannomutase-2 deficiency: CDG-Ia or PMM2-CDG) and Ib (phosphomannose isomerase deficiency: CDG-Ib or MPI-CDG) as measured in leukocytes Follow-up testing for patients with an abnormal transferrin isoform profile This test is not useful for carrier testing.

**Interpretation:** Normal results are not consistent with either phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) or phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib). Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of CDG-Ia. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of CDG-Ib. Mild to moderately reduced enzyme activities will be interpreted in the context of clinical and other laboratory test information submitted with the specimen.

**Reference Values:**

PHOSPHOMANNOMUTASE
PHOSPHOMANNOSE ISOMERASE
Normal >1,300 nmol/h/mg protein


**Phosphorus (Inorganic), Serum**

**Clinical Information:** Of the phosphorus contained in the body, 88% is localized in bone in the form of hydroxyapatite. The remainder is utilized during intermediary carbohydrate metabolism and bound to physiologically important substances such as phospholipids, nucleic acids, and adenosine triphosphate (ATP). Phosphorus exists in blood in the form of inorganic phosphate and organically bound phosphoric acid. The small amount of extracellular organic phosphorus is found exclusively in the form of phospholipids. Serum contains approximately 2.5 to 4.5 mg/dL of inorganic phosphate (the fraction measure in routine biochemical assays). Serum phosphate concentrations are dependent on dietary intake and regulation by hormones such as parathyroid hormone (PTH) and 1,25 vitamin D, and systemic acid base status and may vary widely. Hypophosphatemia may have 4 general causes: shift of phosphate from extracellular to intracellular, renal phosphate wasting, loss from the gastrointestinal tract, and loss from intracellular stores. Hyperphosphatemia is usually secondary to an inability of the kidneys to excrete phosphate and is common in patients with chronic kidney disease stage 4 or greater. Acute hyperphosphatemia can occur as a result of tissue breakdown such as rhabdomyolysis. Other possible contributory factors are increased intake, especially in combination with chronic kidney disease, or a shift of phosphate from tissues into the extracellular fluid.

**Useful For:** Diagnosis and management of a variety of disorders including bone, parathyroid, and kidney disease

**Interpretation:** Hypophosphatemia is relatively common in hospitalized patients. Serum concentrations of phosphate between 1.5 and 2.4 mg/dL may be considered moderately decreased and are not usually associated with clinical signs and symptoms. Levels below 1.5 mg/dL may result in muscle weakness, hemolysis of red cells, coma, bone deformity, and impaired growth. The most acute problem associated with rapid elevations of serum phosphate levels is hypocalcemia with tetany, seizures, and hypotension. Soft tissue calcification is also an important long-term effect of high phosphorus levels. Phosphorus levels below 1.0 mg/dL are potentially life-threatening and are considered a critical value in the Mayo Health System.

**Reference Values:**

<table>
<thead>
<tr>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 years</td>
<td>4.3-5.4 mg/dL</td>
</tr>
<tr>
<td>5-13 years</td>
<td>3.7-5.4 mg/dL</td>
</tr>
<tr>
<td>14-15 years</td>
<td>3.5-5.3 mg/dL</td>
</tr>
</tbody>
</table>

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16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are less than 12 months of age.

Females
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are less than 12 months of age.

Clinical References:

Phosphorus, 24 Hour, Urine

Clinical Information: Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption and consequent urine excretion. Factors that increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake, and proximal tubule defects (eg, Fanconi Syndrome, X-linked hypophosphatemic Rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients.

Useful For: Evaluation of hypo- or hyper-phosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorus excretion is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration.

Reference Values:
> or =18 years: 226-1,797 mg/24 hours
Reference values have not been established for patients who are less than 18 years of age.

Clinical References:

Phosphorus, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolarity, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or
drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars. There are multiple potential causes of osmotic diarrhea. Measurement of phosphate and/or magnesium in liquid stool can assist in identifying intentional or inadvertent use of magnesium and/or phosphate-containing laxatives as the cause. The other causes of osmotic diarrhea include ingestion of osmotic agents such as sorbitol or polyethylene glycol laxatives, or carbohydrate malabsorption due most commonly to lactose intolerance. Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6). Non-osmotic causes of diarrhea include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia. Secretory diarrhea is classified as non-osmotic and is caused by disruption of epithelial electrolyte transport when secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin are present. The fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (<50 mOsm/kg). Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms >4 weeks).

**Useful For:** Workup of cases of chronic diarrhea Identifying the use of phosphate-containing laxatives contributing to osmotic diarrhea

**Interpretation:** Phosphorus elevation above 102 mg/dL is suggestive of phosphate-induced diarrhea.

**Reference Values:**

An interpretive report will be provided

**Clinical References:**

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**Phosphorus, Random, Urine**

**Clinical Information:** Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption and consequent urine excretion. Factors that increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake, and proximal tubule defects (eg, Fanconi syndrome, X-linked hypophosphatemic rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients. A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children.

**Useful For:** Evaluation of hypo- or hyperphosphatemic states Evaluation of patients with nephrolithiasis

**Interpretation:** Interpretation of urinary phosphorous excretion is dependent upon the clinical situation and should be interpreted in conjunction with the serum phosphorous concentration.

**Reference Values:**

No established reference values

Random urine phosphorus may be interpreted in conjunction with serum phosphorus, using both values to calculate fractional excretion of chloride.

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RPHOC

Phosphorus, Random, Urine

Clinical Information: Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption and consequent urine excretion. Factors that increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake, and proximal tubule defects (eg, Fanconi syndrome, X-linked hypophosphatemic rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients. A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children.

Useful For: Evaluation of hypo- or hyperphosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorous excretion is dependent upon the clinical situation and should be interpreted in conjunction with the serum phosphorous concentration.

Reference Values:

No established reference values

Random urine phosphorus may be interpreted in conjunction with serum phosphorus, using both values to calculate fractional excretion of chloride.

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The calculation for fractional excretion (FE) of phosphorus is

\[ \text{FE}(P) = \left( \frac{\text{P(ureine)} \times \text{Creat(serum)}}{\text{P(serum)} \times \text{Creat(ureine)}} \right) \times 100 \]

**Clinical References:**

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**PHTDP 71482**  
**Phosphorylated TDP43 Immunostain, Technical Component Only**

**Clinical Information:** TAR DNA-binding protein 43 (TDP-43) has multiple functions in transcriptional repression, translational regulation, and pre-mRNA splicing. In normal cells, TDP-43 is found in the nucleus, whereas in affected cells TDP-43 is phosphorylated and found in inclusions and neurites. The phosphoTDP-43-specific antibody will only stain the intracytoplasmic inclusions and neurites, thus highlighting the patterns that are hallmarks for amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration.

**Useful For:** Identification of pathological forms of TDP-43 in neurodegenerative diseases

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**PAHD 82786**  
**Phthalic Anhydride, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to phthalic anhydride Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to pig Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

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**Useful For:** Establishing the diagnosis of an allergy to pigeon feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**Pigeon/Dove Droppings Gel Diffusion**

**Clinical Information:** The measurement of serum precipitins by gel diffusion is a commonly used technique to assess exposure and sensitization to various antigens. They are usually of the IgG or IgM class.

**Interpretation:** The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

**Reference Values:**

Negative

**PIN2 (p63/p504S) Immunostain, Technical Component Only**
**Clinical Information:** Prostatic intraepithelial neoplasia (PIN) cocktail-2 is a cocktail including 2 antibodies directed against p63 (nuclear) and P504S (cytoplasm) used in the diagnosis of high-grade PIN and prostate cancer. p63 stains the nuclei of normal myoepithelial cells that surround the prostatic epithelial cells. This myoepithelial layer is lost in carcinoma. P504S is abnormally expressed in high-grade PIN and prostate cancer epithelial cells, but is normally expressed in epithelial cells of the renal tubules, gall bladder and bronchi, and in hepatocytes.

**Useful For:** Aids in the identification of high-grade prostatic intraepithelial neoplasia and prostate cancer

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Pine Nut, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to pine nut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 2024
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive  Reference values apply to all ages.


FPINP 75410
Pine Ponderosa IgE
Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 Positive 4 17.50 - 49.99 Strong Positive 5 50.00 - 99.99 Very Strong Positive 6 >99.99 Very Strong Positive
Reference Values: <0.35 kU/L

FPIAP 57670
Pineapple IgG
Interpretation:
Reference Values: Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PNAP 82815
Pineapple, IgE, Serum
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Establishing a diagnosis of an allergy to pineapple Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or...
anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
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<td>Strongly positive</td>
</tr>
</tbody>
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Reference values apply to all ages.


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**Pinworm Exam, Perianal**

**Clinical Information:** Enterobius vermicularis, also known as pinworm, is a common intestinal nematode with a worldwide distribution. In the United States, pinworm infection is the most common helminth infection of humans and is most frequently found in young school-age children. Transmission is by the fecal-oral route. Individuals become infected when inadvertently ingesting pinworm eggs from the environment (eg, contaminated objects and surfaces). The eggs then hatch in the small intestine and the adults reside in the lumen of the cecum. Gravid adult females migrate to the perianal area during the night and deposit large numbers of eggs in the perianal area, using a glue-like substance to promote adherence to anal skin folds. Most infections are asymptomatic. When present, the most common symptom is nocturnal pruritus ani (nightly anal itching) from the host inflammatory reaction to the eggs and associated adhesion. With itching, the eggs contaminate the fingers of the host and then spread into the environment to infect others. Autoinoculation is also common. Heavy infections may be associated with irritability, difficulty sleeping, abdominal pain, nausea, and vomiting. Ectopic migration of the adult female worm may also lead to vulvovaginitis, salpingo-oophoritis, peritonitis, and, possibly, appendicitis. Pinworm infection is best diagnosed through identification of eggs, and occasionally adults, obtained from the perianal skin folds. This is classically accomplished via collection with clear adhesive cellophane tape. The pinworm paddle (eg, Swube device) facilitates this collection and is provides a safer and more reliable means of collection and examination. To collect eggs with the pinworm paddle, the adhesive side of the paddle is pressed firmly and repeatedly to the perianal region and then returned to its plastic tube for safe transportation to the laboratory. The specimen should be collected first thing in the morning, before the patient bathes or defecates. When the paddle arrives in the laboratory, it is placed on a glass slide and examined using a light microscope for eggs and adult worms. Care must be taken when collecting and examining the specimen, as pinworm eggs are infectious within 4 to 6 hours of being laid. Repeat testing may be recommended to increase the sensitivity of detection in cases of light infection. Several agents are effective in treating pinworm infection (pyrantel pamoate, mebendazole), and good personal hygiene will prevent transmission of the eggs.

**Useful For:** Detection of the eggs of Enterobius vermicularis on the skin of the perianal folds
Interpretation: Positive results are provided indicating the presence of eggs of Enterobius vermicularis.

Reference Values:
Negative (reported as positive or negative)


PIPA
81326

Pipecolic Acid, Serum

Clinical Information: Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine-dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

Useful For: Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Detecting abnormal elevations of pipecolic acid in serum

Interpretation: Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as plasma C22-C26 very long-chain fatty acids, phytanic acid, and pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum); red blood cell plasmalogens; and bile acid intermediates.

Reference Values:
<6 months: < or =6.0 nmol/mL
6 months-<1 year: < or =5.9 nmol/mL
1-17 years: < or =4.3 nmol/mL
> or =18 years: < or =7.4 nmol/mL


PIPU
81248

Pipecolic Acid, Urine

Clinical Information: Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized...
in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore PA analysis is useful for differentiating between these two groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoisoadipic semialdehyde dehydrogenase deficiency (pyridoxine dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

**Useful For:** Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Detecting abnormal elevations of pipecolic acid in urine

**Interpretation:** Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as plasma C22-C26 very long-chain fatty acids, phytanic acid, pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum); RBC plasmalogens; and bile acid intermediates.

**Reference Values:**
- < or =31 days: < or =223.8 nmol/mg creatinine
- 32 days-5 months: < or =123.1 nmol/mg creatinine
- 6 months-11 months: < or =45.0 nmol/mg creatinine
- > or =1 year: < or =5.7 nmol/mg creatinine

**Clinical References:**

### PISTA

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to pistachio Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**PIT1**

**PIT-1 Immunostain, Technical Component Only**

**Clinical Information:** Pit-1, also known as POU1F1, is a transcription factor involved in the development of the anterior pituitary and is useful in the classification of pituitary adenomas. Expression of Pit-1 is observed in somatotropic hormone-producing tumors (prolactin, growth hormone, or thyroid-stimulating hormone).

**Useful For:** Classification of pituitary adenomas

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**

NA

**Clinical References:**

**PLAP**

**Placental Alkaline Phosphatase (PLAP) Immunostain, Technical Component Only**

**Clinical Information:** Placental alkaline phosphatase (PLAP) is expressed in cytotrophoblasts,
syncytiotrophoblasts, and intermediate trophoblast cells. PLAP has been shown to be positive in various tumors, particularly germ-cell tumors and adenocarcinomas. PLAP expression has been described in tumors of Mullerian derivation, pulmonary and colonic carcinomas, and renal cell carcinomas.

**Useful For:** Aids in the identification of germ cell tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**Plaice, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to plaice Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Plasma Cell Assessment, Blood

Clinical Information: Plasma cell proliferative disorders are a group of hematologic neoplasms, all of which are derived from clonal plasma cells. These disorders exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma, a disease that most often is aggressive with poor long-term survival. Detecting plasma cell immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains) is an important element in assessing plasma cell clonality and, hence, establishing the diagnosis. Furthermore, a greater degree of peripheral blood involvement by these disorders is associated with more aggressive disease types and, therefore, is an adverse prognostic indicator. Flow cytometric immunophenotyping (FCIP) is a recognized method for detecting plasma cell Ig light chain restriction. However, shortcomings of this technique, as traditionally performed, include its relative insensitivity and its consistent underestimation of the number of clonal plasma cells present. Both of these short-comings are likely attributable to limitations of the instruments and antibodies used, as well as the presence of intraclonal phenotypic heterogeneity, which created difficulties in accurately detecting and enumerating all of the clonal plasma cells. For this reason, the FCIP plasma cell clonality assessment previously performed in our laboratory was supplemented with a slide-based immunofluorescence technique. However, recent advances in flow cytometry have led to the development of more powerful instruments and antibody reagents that allow for the use of greater antibody combinations and increased resolution of the data. With these tools, the ability of FCIP to detect and enumerate plasma cell clones has been greatly enhanced, allowing us to discontinue the supplemental, labor-intensive, slide-based plasma cell evaluation in peripheral blood specimens. The following algorithms are available in Special Instructions: Laboratory Screening Tests for Suspected Multiple Myeloma-Laboratory Approach to the Diagnosis of Amyloidosis

Useful For: Detecting peripheral blood involvement by plasma cell proliferative disorders
Establishing the diagnosis of and determining prognosis for plasma cell proliferative disorders

Interpretation: In normal peripheral blood specimens, no clonal plasma cells are present (polytypic or too few to detect). Plasma cells are CD38 and CD138 positive. Normal (polyclonal, nonneoplastic) plasma cells are typically CD19-positive, whereas neoplastic (clonal) plasma cells typically are CD19-negative. CD19 expression is especially helpful in distinguishing clonal from nonclonal plasma cells when few analyzable cells are present. CD45 may be expressed by both normal and neoplastic plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population. The evaluation of these antigens aids in the identification of abnormal plasma cells, however, they will not be reported independently.

Reference Values:
CD38+/CD138+ plasma cells=0.0


Plasma Cell DNA Content and Proliferation, Bone Marrow

Clinical Information: Plasma cell proliferative disorders are a group of plasma cell derived clonal hematologic neoplasms that exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma (MM), a disease that is often aggressive with poor long-term survival. Detecting plasma cell clonality through demonstrating immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains), supplemented by the plasma cell immunophenotype and DNA index, is an important element in establishing the diagnosis. It is important to correctly classify patients with plasma cell proliferative disorders as the various disease entities are treated differently. A number of factors are used for this classification including the proportions of clonal bone marrow plasma cells, the DNA index of the clonal plasma cells, and their proliferative activity. The plasma cell DNA index and proliferation assessment by flow cytometry are rapid and reliable. This information can be used to distinguish patients with overt active MM from less aggressive diseases such as MGUS and smoldering MM. Furthermore, in combination with other laboratory data, the results of these studies can be used as a measure of disease aggressiveness in newly diagnosed MM and also to determine therapeutic efficacy and detect disease relapse in treated MM patients. The following algorithms are available in Special Instructions: -Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

Useful For: Establishing a diagnosis of a plasma cell proliferative disorder Providing prognostic information for newly diagnosed multiple myeloma and other plasma cell proliferative disorders Assessing response to therapy and detecting disease relapse and progression in treated plasma cell proliferative disorder patients Determining plasma cell DNA content and proliferation

Interpretation: Plasma Cell Clonality: Plasma cell populations with a kappa to lambda ratio of either greater than 3.9 or less than 0.5 will be considered either kappa or lambda immunoglobulin light chain restricted (monotypic), respectively. As, in rare instances, immunoglobulin light chain restricted plasma cell populations may be polyclonal at the genetic level, the term monotypic rather than monoclonal plasma cells will be used. In addition to immunoglobulin light chain expression, other data collected will be used to supplement the detection of abnormal plasma cell populations. In plasma cells, CD19 expression is associated with the presence of benign, polyclonal cell populations. Therefore CD19 expression will be used as a secondary element in detecting clonal plasma cells. While loss of plasma cell CD45 expression is associated with neoplasia, CD45 is expressed by both normal and neoplastic plasma cells. Therefore, absence of plasma cell CD45 expression will be used as an aid in detecting abnormal plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population, therefore inclusion of antibodies to this antigen allows for more sensitive detection of both subtypes. In addition, as DNA content will be simultaneously assessed, the detection of plasma cell aneuploidy will also serve as a tool for identifying abnormal plasma cell populations. These additional immunophenotypic tools for identifying abnormal plasma cells will increase the sensitivity of the method beyond examining light chain expression; particularly in biclonal plasma cell proliferative disorders in which there are both kappa and lambda immunoglobulin light chain expressing subsets. Plasma Cell Proliferation: The proportion of plasma cells in S-phase will be determined by measuring the proportion of cells with DNA content between the G0/G1 and G2/M peaks. In some instances, plasma cell proliferation will not be able to be determined by this method, including when there are fewer than 300 abnormal plasma cell events and when there are multiple aneuploid plasma cell populations. In newly diagnosed multiple myeloma, a plasma cell S-phase of greater than 2.0%, is associated with a more aggressive disease course; this value is published standard for identifying plasma cell neoplasms with a high proliferative rate, it will be noted in the report if the estimated S-phase exceeds this value.) DNA Index: Processed cells are stained with DAPI (4’,6-diamidino-2-phenylindole) to determine the DNA index of the abnormal plasma cells. This will be determined by dividing the measured DNA content of the G0/G1 abnormal plasma cells by the DNA content of the normal G0/G1 plasma cells present. For this determination, normal plasma cells are the optional control cell population due to similarities in nuclear and overall cell size. Plasma cells with a G0/G1 DNA content index of less than 0.95 will be considered hypodiploid (worst prognosis); those with a G0/G1 DNA content index of greater than 1.05 will be considered hyperdiploid (favorable prognosis). Plasma cells with a DNA index of 1.9 to 2.1 will be considered tetraploid (non-favorable prognosis) if a confirmatory G2/M population with a DNA index of 4 is identified. As noted above, since normal plasma cells are neither hyper- nor hypodiploid, DNA index will be used as a supplemental tool in detecting clonal plasma cells. Percent
Polyclonal Plasma Cells in Total Plasma Cells: It has been shown that higher percent polyclonal plasma cells in total plasma cells can mean longer progression-free survival, higher response rates, and lower frequency of high-risk cytogenetics abnormalities. Studies have also shown a higher incidence of polytypic plasma cells in monoclonal gammopathy of uncertain significance and smoldering myeloma in comparison to multiple myeloma.

Reference Values:
Plasma Cell Clonality:
Normal bone marrow
No monotypic clonal plasma cells detected

DNA Index:
Normal polypotpic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05


Plasma Cell Proliferative Disorder, FISH, Bone Marrow

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell proliferative disorders (PCPD): monoclonal gammopathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over age 50 years, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders Identifying prognostic markers based on the abnormalities found

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds
the normal reference range for any given probe.

Reference Values:
An interpretive report will be provided.


PLASF 35293

Plasma Cell Proliferative Disorder, FISH, Tissue

Clinical Information: A plasmacytoma is a localized proliferation of plasma cells that are cytologically and immunophenotypically identical to the plasma cell clones seen in myeloma. There are 2 primary types of plasmacytomas: solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EP). SPBs are a localized bone tumor comprised of plasma cells and account for about 5% of all plasma cell neoplasms. Common sites for SPBs are the vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula. Patients often present with pathological fracture or bone pain near the lesion. Treatment is typically radiation therapy; at 10 years, 35% of patients appear to be cured, 55% develop myeloma, and 10% have local recurrence. EPS are tumors of plasma cells that form in areas away from the bone and account for 3% to 5% of all plasma cell neoplasms. Approximately 80% of EPS occur in the upper respiratory tract. Less common locations include the gastrointestinal tract, bladder, testis, central nervous system, and skin. Treatment consists of radiation therapy. Regional recurrence develops in about 25% of patients, but development of myeloma is less frequent, occurring in only about 15% of patients. Genetics of both types of plasmacytomas, while not extensively studied, appear to be the same as plasma cell myeloma. Paraffin plasma cell fluorescence in situ hybridization (FISH) evaluation of bone marrow clot specimens is also important when a fresh bone marrow specimen is not available or is unsuccessful in the initial/diagnostic evaluation to document the genetic abnormalities associated with a patient’s plasma cell clone.

Useful For: Supporting the diagnosis of plasmacytoma or myeloma when coordinated with a surgical pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a plasmacytoma or myeloma. A negative result does not exclude the diagnosis of a plasmacytoma or myeloma.

Reference Values:
An interpretive report will be provided.

Plasma Cell Proliferative Disorder, Pre-Analysis Cell Sorting, Bone Marrow

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are four main categories of plasma cell proliferative disorders (PCPD): monoclonal gammopathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over age 50 years, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders Sorting plasma cells for FISH analysis

Interpretation: Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

Reference Values:
Only orderable as a reflex. See PCPDS / Plasma Cell Proliferative Disorder, FISH, Bone Marrow

An interpretive report will be provided.


Plasma Free Hemoglobin, Plasma

Clinical Information: Hemoglobin is contained within erythrocytes and significant amounts of “free hemoglobin” (outside the RBC) are not normally present in plasma. This free hemoglobin is also called plasma hemoglobin. Normal blood draw procedures cause a limited degree of unavoidable disruption and therefore a small amount of free hemoglobin may be present in normal people. When detectable, the total plasma hemoglobin and a subcomponent, oxyhemoglobin, are both reported.
Significant amounts of free hemoglobin occur in plasma following disruption of the RBC for any reason. This might result from a transfusion reaction or mechanical fragmentation of RBCs due to instrumentation, surgical procedures, or mechanical devices. Patients requiring support from extracorporeal membrane oxygenation (ECMO) or centrifugal ventricular assist devices (cVAD) are commonly monitored for trends in plasma free hemoglobin levels to assess for increasing hemolysis. Sharp spikes in plasma hemoglobin levels can indicate pump disruption. However, plasma hemoglobin can be artifactually increased due to a traumatic blood draw or prolonged exposure to post-draw RBCs. Additionally, bilirubin interferes substantially with the ability to calculate total plasma hemoglobin levels and results may be spurious and unreliable. This is a difficulty frequently encountered in serially tested patients. When this occurs, the oxyhemoglobin level tends to show less interference and will be the only analyte reported in the presence of increased bilirubin (>5 mg/dL). When using trending data, total plasma hemoglobin and oxyhemoglobin levels are not interchangeable and should be compared within their subgroups only.

**Useful For:** Determining whether hemolysis is occurring such as from:
- Transfusion reaction
- Mechanical fragmentation of red blood cells
- Relative comparison to baseline levels in extracorporeal membrane oxygenation (ECMO) and centrifugal ventricular assist device (cVAD) patients to assess pump disruption

**Interpretation:** An elevation in plasma hemoglobin above the reference range indicates likely intravascular hemolysis due to one of the causes listed in the Useful For section.

**Reference Values:**

### TOTAL PLASMA HEMOGLOBIN

- > or =12 months: 0.0-15.2 mg/dL

Reference values have not been established for patients who are <12 months of age.

### OXYHEMOGLOBIN

- > or =12 months: 0.0-12.4 mg/dL

Reference values have not been established for patients who are <12 months of age.

**Clinical References:**


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**Plasmalogens, Blood**

**Clinical Information:** Peroxisomes are organelles that carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytic acid, and biosynthesis of plasmalogens and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and disorders of peroxisome function with single peroxisomal enzyme/transporter defects where the organelle is intact, but a specific function is disrupted. Biochemical abnormalities in peroxisomal biogenesis disorders can include accumulations of VLCFA, phytanic, and pristanic acid, piperolic acid, bile acids, and reduced plasmalogens. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, phytanic acid, and its metabolite pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum; or POXP / Fatty Acid Profile, Peroxisomal [C22-C26], Plasma), piperolic acid (PIPA / Picrolic Acid, Serum; or PIPU / Picrolic Acid, Urine), bile acids (BAIPD / Bile Acids for Peroxisomal Disorders, Serum), and plasmalogens. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders, which are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata (RCDP) is a
malformation disorder characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia punctata. Currently, there are 5 clinical types of rhizomelic chondrodysplasia punctata: RCDP 1, 2, 3, 4 (also known as FAR1 deficiency) and 5. RCDP 1 is the classical form that presents in infancy with skeletal manifestations including rhizomelic shortening, cataracts, and severe to profound postnatal growth deficiency. Infants with RCDP 1 have developmental delay, and later, intellectually disability. The majority of children with RCDP 1 do not survive beyond the first decade of life. RCDP 1 is an autosomal recessive disorder caused by pathogenic variants in the PEX7 gene. RCDP 2 and 3 have clinical phenotypes similar to RCDP 1 and may be distinguished by plasmalogenn deficiency. RCDP 2 and 3 are autosomal recessive conditions caused by pathogenic variants in GNPAT and AGPS genes, respectively. Individuals with RCDP 5 have a milder phenotype when compared to classic RCDP 1, with most individuals able to achieve self-feeding, independent ambulation, and development of limited language skills. RCDP5 results in less pronounced reduction in plasmalogens compared to RCDP 1. This newly recognized subtype of RCDP is an autosomal recessive disorder caused by pathogenic variants in the PEX5 gene. The typical biochemical profile for RCDP shows reduced plasmalogens, elevated phytanic acid, and normal VLCFA. Confirmatory testing via molecular analysis for all types of RCDP is available (PDGP / Peroxisomal Disorder Gene Panel, Varies). Fatty acyl-CoA reductase 1 (FAR1) deficiency, also known as RCDP type 4, is an autosomal recessive peroxisomal disorder caused by pathogenic variants in the FAR1 gene that result in early-onset epilepsy, microcephaly, cataracts, postnatal growth deficiency, and intellectual disability. Unlike RCDP, however, infants with FAR1 deficiency have no skeletal abnormalities. The biochemical profile for FAR1 deficiency includes reduced plasmalogens, normal to elevated phytic acid, and normal VLCFA.

Useful For: Diagnosing patients with possible peroxisomal disorders, such as peroxisomal biogenesis disorders (Zellweger syndrome spectrum) and rhizomelic chondrodysplasia punctata (RCDP), including fatty acyl-CoA reductase 1 (FAR1) deficiency Evaluating patients with abnormal newborn screen results for X-linked adrenoleukodystrophy who appear to have a different type of peroxisomal disorder, such as a Zellweger syndrome spectrum disorder. Aiding in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C16:0, C18:0 and C18:1 plasmalogens and the ratio of the C16:0 and C18:0 plasmalogens to the respective fatty acid. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of reduced plasmalogens and abnormal very long-chain fatty acids (VLCFA), as well as possible abnormalities in pipecolic acid and bile acids, can be consistent with a diagnosis of a peroxisomal biogenesis disorder (Zellweger syndrome spectrum). A profile of reduced plasmalogens, elevated phytanic acid, and normal VLCFA is consistent with a diagnosis of rhizomelic chondrodysplasia punctata, such as RCDP type 1 or 2, FAR1 deficiency (RCDP type 4), or other types of RCDP. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

Reference Values:
Hexadecanal-Dimethylacetal, C16:0 DMA:
> or =6.00 mcg/mL

Octadecanal-Dimethylacetal, C18:0 DMA:
> or =9.00 mcg/mL

9Z-Octadecenal-DiMe acetal C18:1DMA:
> or =2.00 mcg/mL

C16:0 DMA/C16:0:
> or =0.018

C18:0 DMA/C18:0:
> or =0.040


Plasmalogens, Blood Spot

**Clinical Information:** Peroxisomes are organelles that carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids ( VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and disorders of peroxisome function with single peroxisomal enzyme/transporter defects where the organelle is intact, but a specific function is disrupted. Biochemical abnormalities in peroxisomal biogenesis disorders can include accumulations of VLCFA, phytanic, and pristanic acid, pipecolic acid, bile acids, and reduced plasmalogens. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, phytanic acid, and its metabolite pristanic acid (POX / Fatty Acid Profile, Peroxosomal [C22-C26], Serum or POXP / Fatty Acid Profile, Peroxosomal [C22-C26], Plasma), pipecolic acid (PIPA / Pipecolic Acid, Serum or PIPU / Pipecolic Acid, Urine), bile acids (BAIPD / Bile Acids for Peroxisomal Disorders, Serum), and plasmalogens. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders, which are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata (RCDP) is a malformation disorder characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia punctata. Currently, there are 5 clinical types of rhizomelic chondrodysplasia punctata: RCDP 1, 2, 3, 4 (also known as FAR1 deficiency) and 5. RCDP 1 is the classical form that presents in infancy with skeletal manifestations including rhizomelic shortening, cataracts, and severe to profound postnatal growth deficiency. Infants with RCDP 1 have developmental delay, and later, intellectually disability. The majority of children with RCDP 1 do not survive beyond the first decade of life. RCDP 1 is an autosomal recessive disorder caused by pathogenic variants in the PEX7 gene. RCDP 2 and 3 have clinical phenotypes similar to RCDP 1 and may be distinguished by plasmalogen deficiency. RCDP 2 and 3 are autosomal recessive conditions caused by pathogenic variants in GNPAT and AGPS genes, respectively. Individuals with RCDP 5 have a milder phenotype when compared to classic RCDP 1, with most individuals able to achieve self-feeding, independent ambulation, and development of limited language skills. RCDP5 results in less pronounced reduction in plasmalogens compared to RCDP 1. This newly recognized subtype of RCDP is an autosomal recessive disorder caused by pathogenic variants in the PEX5 gene. The typical biochemical profile for RCDP shows reduced plasmalogens, elevated phytanic acid, and normal VLCFA. Confirmatory testing via molecular analysis for all types of RCDP is available (PDGP / Peroxisomal Disorder Gene Panel, Varies). Fatty acyl-CoA reductase 1 (FAR1) deficiency, also known as RCDP type 4, is an autosomal recessive disorder caused by pathogenic variants in the FAR1 gene that result in early-onset epilepsy, microcephaly, cataracts, postnatal growth deficiency, and intellectual disability. Unlike RCDP, however, infants with FAR1 deficiency have no skeletal abnormalities. The biochemical profile for FAR1 deficiency includes reduced plasmalogens, normal to elevated phytanic acid, and normal VLCFA.

**Useful For:** Diagnosing patients with possible peroxisomal disorders, such as peroxisomal biogenesis disorders (Zellweger syndrome spectrum) and rhizomelic chondrodysplasia punctata (RCDP), including fatty acyl-CoA reductase 1 (FAR1) deficiency. Evaluating patients with abnormal newborn screen results for X-linked adrenoleukodystrophy who appear to have a different type of peroxisomal disorder such as a Zellweger syndrome spectrum disorder. Aiding in the assessment of peroxisomal function

**Interpretation:** Reports include concentrations of C16:0, C18:0 and C18:1 plasmalogens and the ratio
of the C16:0 and C18:0 plasmalogens to the respective fatty acid. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of reduced plasmalogens and abnormal very long-chain fatty acids (VLCFA), as well as possible abnormalities in phytic acid and bile acids, can be consistent with a diagnosis of a peroxisomal biogenesis disorder (Zellweger syndrome spectrum). A profile of reduced plasmalogens, elevated phytic acid, and normal VLCFA is consistent with a diagnosis of rhizomelic chondrodysplasia punctata, such as RCDP type 1 or 2, FAR1 deficiency (RCDP type 4), or other types of RCDP. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

**Reference Values:**

**Hexadecanal-Dimethylacetal, C16:0 DMA**

\[ > = 7.00 \text{ mcg/mL} \]

**Octadecanal-Dimethylacetal, C18:0 DMA**

\[ > = 12.00 \text{ mcg/mL} \]

**9Z-Octadecenal-DiMe acetal C18:1DMA**

\[ > = 2.00 \text{ mcg/mL} \]

**C16:0 DMA/C16:0**

\[ > = 0.012 \]

**C18:0 DMA/C18:0**

\[ > = 0.050 \]

**Clinical References:**


**FPAI1** 75736

**Plasminogen Activator Inhibitor 1 (PAI-1) Antigen**

**Reference Values:**

4.0 - 43.0

**FPAIG** 75142

**Plasminogen Activator Inhibitor-1, 4G/5G Genotyping (PAI-1 Polymorphism)**

**Clinical Information:** The PAI-1 4G allele is an inherited characteristic. If the polymorphism is present in a heterozygous or homozygous fashion, we recommend that the patient and their family consider genetic counseling to obtain additional information on inheritance and to identify other family members at risk. If a patient possesses two or more congenital or acquired risk factors, the risk of disease may rise to more than the sum of the risk ratios for the individual risk factors. For instance, a combination of the 4G/4G genotype and the insulin resistance syndrome may confer an increase in cardiovascular disease risk over that conferred by the presence of an isolated PAI-1 4G/4G polymorphism.

**Plasminogen Activity, Plasma**

**Clinical Information:** During the formation of a hemostatic (fibrin) plug, biochemical mechanisms are initiated to limit the extent of the hemostatic process at the site of injury and maintain vascular patency. This process of fibrinolysis is defined as the plasmin-mediated degradation of fibrin. Plasmin limits the extent of the hemostatic process at the site of vessel injury. Plasmin is generated from its precursor, plasminogen, by plasminogen activators (ie, tissue plasminogen-activator: tPa; urokinase-type plasminogen activator: uPa). Plasminogen is a single-chain glycoprotein that is synthesized in the liver and has a biologic half-life of approximately 2 days. Deficiency of plasminogen may be inherited or acquired. Persons with congenital plasminogen deficiency are at an increased risk for development of an ocular condition called ligneous conjunctivitis. Congenital deficiency of plasminogen is autosomal transmitted and rare in the general population, with a prevalence of approximately 0.4%. Based on the results of functional and immunologic (antigenic) assays, 2 types of plasminogen deficiency have been identified: -Quantitative deficiency (type I)-defined by a corresponding decrease in both plasminogen activity and antigen level -Functional deficiency (type II)-caused by a normally synthesized but dysfunctional plasminogen This plasminogen activity assay will identify both types of deficiency. Acquired causes of plasminogen deficiency include consumption such as with thrombolytic therapy (urokinase, tPa) or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), or decreased synthesis (liver disease).

**Useful For:** Evaluating patients with ligneous conjunctivitis (strong association with homozygous plasminogen deficiency) Evaluating fibrinolysis, in combination with other components of the fibrinolytic system (fibrinogen, tissue plasminogen-activator-inhibitor, and d-dimers)

**Interpretation:** Plasminogen activity below 75% may represent a congenital deficiency state, if acquired deficiency can be excluded. Hereditary abnormalities of plasminogen (deficiency or dysfunction) are very uncommon. Acquired causes of plasminogen deficiency are much more common and may be the result of consumption due to thrombolytic therapy or intravascular coagulation and fibrinolysis or decreased synthesis (ie, liver disease). Plasminogen levels are low at birth (approximately 50% of adult normal level) and reach adult levels at 6 months of age.

**Reference Values:**
75-140%


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**Platelet Antibody Screen, Serum**

**Clinical Information:** Platelet antibodies may be allo- or autoantibodies and may be directed to a wide range of antigenic "targets" carried on platelet cytoplasmic membranes. Serum platelet antibody test is optimized to identify the presence of platelet allo-antibodies in the patient. Platelet alloantibodies are involved in several clinical situations such as: -Immune mediated refractoriness to platelet transfusions usually due to antibodies to HLA class I and sometimes to antibodies specific to platelet antigens. -Neonatal alloimmune thrombocytopenia (NAIT) -Posttransfusion purpura (PTP), which are usually associated with platelet-specific antibodies This test is not recommended for the diagnosis of immune thrombocytopenia (ITP) or autoimmune thrombocytopenia. Tests that are optimized to detect antibodies bound to the platelets will be useful in these situations; cell-bound platelet antibody (Direct) test is strongly recommended instead (CBPAN / Cell Bound Platelet Auto-Antibody Screen, Blood).

**Useful For:** Detecting alloantibodies to epitopes on platelet glycoproteins IIb/IIIa, Ib/Ix, Ia/IIa, IV and HLA Class I antigens to evaluate cases of immune mediated refractoriness to platelet transfusions,
Posttransfusion purpura, or neonatal alloimmune thrombocytopenia

Reference Values:
Not applicable

Clinical References:

Platelet Neutralization Procedure, Plasma

Clinical Information: Prolonged clotting times may be due to a variety of factors including the presence of clotting factor deficiencies, factor inhibitors, and lupus anticoagulants (antiphospholipid antibodies). When a prolonged activated partial thromboplastin time (APTT) demonstrates inhibition on mixing with normal plasma indicative of presence of an inhibitor, the platelet neutralization procedure (PNP) is useful in determining if this inhibition is due to presence of a lupus anticoagulant (LAC). The PNP involves the addition of washed, freeze-thawed platelets or buffer to the patient's plasma. An APTT is done on both mixtures and the clotting times are compared. Additional phospholipid supplied by the PNP reagent can absorb LAC, thereby diagnostically shortening the APTT. For performance and interpretation of the PNP, the baseline APTT should be significantly prolonged (preferably at least 3 to 5 seconds above the upper limit of the reference range), and APTT inhibition must be demonstrated or suggested by a mixing study with normal plasma (ie, 1:1 mix fails to shorten into the normal range).

Useful For: Aiding in the confirmation or exclusion of the presence of a lupus anticoagulant (LAC) inhibitor when used in conjunction with other appropriate coagulation tests Aids in differentiating deficiencies or inhibitors of specific coagulation factors (eg, factor VIII inhibitor) from LAC inhibitors

Interpretation: Interpretation of the results of the platelet neutralization procedure (PNP) test is complex and needs to be performed in the context of results of mixing study of the prolonged activated partial thromboplastin time (APTT), the APTT PNP and the buffer control APTT, as well as results of other coagulation tests (eg, prothrombin time and thrombin time as well as available clinical information). Plasma containing lupus anticoagulant (LAC) will demonstrate significant shortening of the prolonged inhibited APTT with the addition of platelets (by at least 4-5 seconds), when compared to baseline APTT, and the buffer control APTT typically will be 4 to 5 seconds longer than the PNP APTT.

Reference Values:
Only orderable as a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

An interpretive report will be provided.

Clinical References:
2. Brandt JT, Barna LK,
Platelet Surface Glycoprotein by Flow Cytometry, Blood

**Clinical Information:** Platelets have essential roles in primary hemostasis. Exposed collagen at a vascular damage site can activate platelets via collagen receptor GPVI and GPIa and bind shear-stretched multimeric VWF proteins, which subsequently interact with the platelet surface receptor, GPIb-V-IX. Upon full activation, platelets can aggregate by binding to fibrinogen through activated GPIIb-GPIIIa receptors. Deficiency of platelet surface glycoproteins can cause bleeding diathesis. Platelet flow cytometric analysis is the preferred method to assess hereditary platelet disorders due to quantitative surface glycoprotein (GP) deficiencies. GP expression levels can be measured by using fluorescent-conjugated GP-specific antibodies and their fluorescent intensities can be compared to normal ranges of various glycoproteins. CD Number Glycoprotein Name Integrin Name CD41 GPIIb Alpha 2b CD42a GPIX NA CD42b GPIb-alpha NA CD49b GPIa Alpha 2 CD61 GPIIIa Beta 3 NA GPVI NA

**Useful For:** Identification of markedly decreased CD41 (GPIIb) and CD61 (GPIIIa) expression levels, which are diagnostic for Glanzmann thrombasthenia. Identification of markedly decreased CD42a (GPIX) and CD42b (GPIb-alpha) expression levels, which are diagnostic for Bernard-Soulier syndrome. Identification of decreased GPVI expression, which suggests collagen receptor deficiency. Identification of decreased CD49b (GPIa), which suggests collagen receptor deficiency.

**Interpretation:** CD Markers % Reference Range Median Comments CD41 and CD61 50%-69% (Marginally) Marginally decreased platelet surface receptors CD41 (GPIIb) and CD61 (GPIIIa) are of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, benign polymorphisms, or a heterozygous state of Glanzmann thrombasthenia. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50%: (Moderately) <30%: (Markedly) Platelet surface expression of CD41 (GPIIb) and CD61 (GPIIIa) are moderately or markedly decreased. This finding is suggestive for a variant of Glanzmann thrombasthenia. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. CD42a and CD42b 50%-69% (Marginally) Marginally decreased platelet surface receptors CD42a (GPIX) and CD42b (GPIb-alpha) are of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, benign polymorphisms, or a heterozygous state of Bernard-Soulier syndrome. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50%: (Moderately) <30%: (Markedly) Platelet surface expression of CD42a (GPIX) and CD42b (GPIb-alpha) are moderately or markedly decreased. This finding is suggestive for a variant of Bernard-Soulier syndrome. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. CD49b 30%-59% (Marginally) Marginally decreased platelet surface receptor CD49b (GPIa) is of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, a benign polymorphism, or a variant of platelet collagen receptor glycoprotein Ia/IIa deficiency. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 10%-30% (moderately) <10% (Markedly) Platelet surface expression of CD49b (GPIa) is moderately or markedly decreased. This finding is suggestive for a variant of a variant of platelet collagen receptor glycoprotein Ia/IIa deficiency. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. GPVI
50%-69% (Marginally) Marginally decreased platelet surface receptor glycoprotein VI (GPVI) is of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, a benign polymorphism or a variant of platelet collagen receptor GPVI deficiency. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50% (moderately) <30% (Markedly) Platelet surface expression of glycoprotein VI (GPVI) is moderately or markedly decreased. This finding is suggestive for a variant of a variant of platelet collagen receptor GPVI deficiency. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated.

Reference Values:
GPIIb CD41: > or =70.0% (Normal Range-Median)
GPIIIa CD61: > or =70.0% (Normal Range-Median)
GPX CD42a: > or =70.0% (Normal Range-Median)
GPIb-alpha CD42b: > or =70.0% (Normal Range-Median)
GPla CD49b: > or =60.0% (Normal Range-Median)


PTEM
Platelet Transmission Electron Microscopic Study, Whole Blood

Clinical Information: Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life threatening. A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Platelet (P) transmission electron microscopy (TEM) has been an essential tool for laboratory diagnosis of various hereditary platelet disorders since it was first used to visualize fibrin-platelet clot formation in 1955. PTEM employs 2 main methods to visualize platelet ultrastructure, whole mount (WM) TEM and thin section (TS) TEM. WM-TEM is considered the gold standard test for diagnosing dense granule deficiencies in Hermansky-Pudlak syndrome, alpha-delta platelet storage pool deficiency, Paris-Trousseau-Jacobsen syndrome, Wiskott-Aldrich syndrome, TAR (thrombocytopenia, absent radii) syndrome, Chediak-Higashi syndrome, and more. TS-TEM is a preferred method to visualize platelet alpha granules, other organelles, and abnormal inclusions. Platelet disorders that can be detected by PTEM include (but are not limited to): Delta granules (dense bodies): -Hermansky Pudlak syndrome -Wiskott-Aldrich syndrome -Chediak Higashi syndrome -Jacobsen/Paris-Trousseau syndrome -York platelet syndrome -Storage pool deficiency, not otherwise specified Alpha granules: -Gray platelet syndrome -White platelet syndrome -X-linked GATA-1 variant -Jacobsen/Paris-Trousseau syndrome Alpha and delta granules: -Alpha-delta storage pool deficiency

Useful For: Diagnosing platelet disorders

Interpretation: Ultrastructural abnormalities identified by platelet transmission electron microscopy (TEM) are evaluated by a Mayo hematopathologist. Platelet size, alpha granules, Golgi complex, and abnormal inclusions will be assessed as part of the morphologic examination under TEM. Distinct and sometimes pathognomonic ultrastructural abnormalities are found in Hermansky Pudlak syndrome, gray platelet syndrome with virtually absent alpha granules, white platelet syndrome, Medich giant platelet disorder, X-linked GATA-1 macrothrombocytopenia, and, recently described, York platelet syndrome.

Reference Values:
Mean dense granules/platelet $\geq 1.2$


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**FPLAT 75450**

**Platinum, Serum**

**Reference Values:**
Reporting limit determined each analysis.

Normally: Less than 1 mcg/L.

Total serum platinum concentrations following administration of platinum-based chemotherapeutics vary based on route of administration, duration of treatment and other pharmacokinetic variables.
Peak concentrations in excess of 2000 mcg/L are common.

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**PLAZO 65855**

**Plazomicin, Plasma**

**Clinical Information:** Plazomicin is an aminoglycoside engineered to overcome the most prevalent aminoglycoside-modifying enzymes, which are a common aminoglycoside-resistance mechanism. Plazomicin levels are intended to be used by clinicians to support clinical decision-making in guiding appropriate dosage adjustments for patients on plazomicin therapy. The safety and effectiveness of plazomicin treatment in an individual patient should ultimately be based on clinical response. The trough reference range represents plazomicin minimum (trough) concentrations associated with a reduced risk of nephrotoxicity. However, some patients with plasma trough concentrations outside the trough reference range may achieve a satisfactory response.

**Useful For:** An aid to achieving the desired plasma concentrations of plazomicin

**Interpretation:** The plazomicin drug package insert should be consulted for information regarding the utilization of plazomicin concentrations and guidance for therapeutic drug monitoring (TDM). For patients with complicated urinary tract infections (cUTI) with creatinine clearance (CLcr) values of 15 and higher, but less than 90 mL/min, monitoring of plazomicin plasma trough concentrations is recommended to avoid potentially toxic levels. For this subset of patients, it is recommended that the sample for the plazomicin minimum (trough) concentration measurement be drawn within approximately 30 minutes before administration of the second dose of plazomicin. Plazomicin dosage should be adjusted to avoid trough levels above 3 mcg/mL. Modeled plazomicin trough concentrations from 377 patients with cUTI in Phase 2 and Phase 3 trials have been determined to range from 0.1 to 3.3 mcg/mL (5-95 percentile range) with a median and geometric mean of 0.8 and 0.7 mcg/mL, respectively. Measured plazomicin trough concentrations by liquid chromatography-tandem mass spectrometry (LC-MS/MS) for 274 trough samples in the Phase 3 Study ACHN-490-009 resulted in similar values (0.2 to 5.7 mcg/mL 5-95 percentile range; 1.1 mcg/mL median and geometric mean). For effective treatment, some patients may require plasma levels outside of these ranges. Therefore, the expected ranges are provided as guidelines, and individual patient results should be interpreted with the aid of the dosage adjustment algorithms in the plazomicin drug package insert and in the context of the patient's other clinical signs and symptoms.

**Reference Values:**
Complicated urinary tract infections (cUTI):
Trough Reference Range: <3 mcg/mL
(Trough=30 min before second dose, and 30 min before subsequent doses as appropriate)

**Clinical References:** 1. McKinnell JA: Improved outcomes with plazomicin compared with colistin in patients with bloodstream infections caused by carbapenem-resistant enterobacteriaceae (CRE): Results
Plum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to plum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Clinical Information:** Acute promyelocytic leukemia (APL) accounts for 5% to 10% of acute myeloid leukemia, and generally has a good prognosis with current treatment protocols. APL cells contain a fusion gene comprised of the downstream sequences of the retinoic acid receptor alpha gene (RARA) fused to the promoter region and upstream sequences of one of several genes, the most common (>80%) being the promyelocytic leukemia gene (PML). The fusion gene is designated PML/RARA and may be seen in a karyotype as t(15;17)(q22;q12). Messenger RNA (PML/RARA) produced from the fusion gene can be detected using a PCR-based assay, and indicates the presence of neoplastic cells. The PCR-based assay has greater sensitivity than standard methods such as morphology review, karyotyping, or FISH. Recent studies have indicated that sensitive monitoring is important because the majority of patients who remain PCR positive, or become PCR positive again following treatment, will relapse and likely benefit from early intervention for residual/recurrent disease. This quantitative assay allows PML/RARA levels to be monitored rather than simply detecting the presence or absence of disease.

**Useful For:** Diagnosis of acute promyelocytic leukemia (APL) Detection of residual or recurrent APL Monitoring the level of promyelocytic leukemia/retinoic acid receptor alpha (PML/RARA) in APL patients

**Interpretation:** The assay is reported in the form of a normalized ratio of promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) fusion transcript to the control gene ABL1 expressed as a percentage, which is an estimate of the level of PML/RARA RNA present in the specimen, expressed in relation to the level of RNA from an internal control gene (ABL1). The normalized ratio has no units but is directly related to the level of PML/RARA detected (ie, larger numbers indicate higher levels of PML/RARA and smaller numbers indicate lower levels). A relative expression value minimizes variability in the RNA levels measured in separate specimens tested at different times. Although a quantitative PCR assay is performed, the precision of the assay is such that results must be considered semiquantitative, and it is recommended that only log changes be considered significant. Critical results, such as a change in the status of positivity, should be repeated on a separate specimen to verify the result.

**Reference Values:**
An interpretive report will be provided.

If positive, a value representing a ratio of PML-RARA fusion transcript to the control gene ABL1 expressed as a percentage will be reported.


**Clinical Information:** This test is appropriate for individuals with clinical features suggestive of Charcot-Marie-Tooth type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP). CMT1A is a dominantly inherited disease characterized progressive distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity starting early in life. Duplications of the PMP22 gene are associated with CMT1A. Deletions of PMP22 are associated with hereditary neuropathy with liability to pressure palsies (HNPP), a dominantly inherited disease resulting in peripheral neuronal demyelination. HNPP is characterized clinically by recurrent focal motor and sensory neuropathy in a single nerve that can manifest as numbness, muscular weakness, and atrophy.

**Useful For:** Diagnosis of Charcot-Marie-Tooth type 1A or hereditary neuropathy with liability to pressure palsies

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or
possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

PMS2I
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PMS2Z
Clinical Information:
Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes, and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability and/or immunohistochemistry for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of PMS2 are more likely to have a germline mutation in the PMS2 gene.

Useful For:
Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer
Determining whether absence of PMS2 protein in tumor tissue, as demonstrated by immunohistochemistry, is associated with a germline mutation in the affected individual
Identification of familial PMS2 mutation to allow for predictive testing in family members

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. (1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretative report will be provided.


PMS2 Immunostain, Technical Component Only

Clinical Information: Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. HNPCC is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the HNPCC spectrum. Several clinical variants of HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair variants (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair alterations, characterized by the presence of biallelic deleterious alterations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals with a personal or family history of cancer suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, variant analysis of the associated gene can be performed to identify the causative germline variant and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between
somatic and germline alterations. Genetic testing of the gene indicated by IHC analysis can help to
distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed,
BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1
Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline
etiology. It should be noted that this HNPCC screen is not a genetic test, but rather stratifies the risk of
having an inherited cancer predisposition syndrome and identifies patients who might benefit from
subsequent genetic testing.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary
nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to
identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test does not include pathologist interpretation, only technical performance of
the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic
evaluation or second opinion of the case. Â The positive and negative controls are verified as showing
appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control
tissue is not included on the slide, a scanned image of the relevant quality control tissue is available
upon request; call 855-516-8404. Â Interpretation of this test should be performed in the context of the
patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
1. Burgart LJ: Testing for defective DNA mismatch repair in colorectal
Hum Pathol. 2010;41:1387-1396
mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin
sebaceous tumors, and gynecologic tract carcinomas. Mod Pathol. 2011;24:1004-1014
immunohistochemistry and molecular biology suggests a role for hMLH6 (correction of hMLH6)
6. Shia J: Immunohistochemistry versus
microsatellite instability testing for screening colorectal cancer patients at risk for hereditary
high frequency of PMS2 defects in colorectal cancer. Gastroenterology. 2005;128:1160-1171

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**Pneumococcal Antibody Panel (12 Serotype)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Pneumococcal Antibody Panel</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Pneumo Ab Type 1</td>
<td>&gt;1.3 ug/mL</td>
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<tr>
<td>Pneumo Ab Type 3</td>
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<td>Pneumo Ab Type 4</td>
<td>&gt;1.3 ug/mL</td>
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<tr>
<td>Pneumo Ab Type 8</td>
<td>&gt;1.3 ug/mL</td>
</tr>
<tr>
<td>Pneumo Ab Type 9 (9N)</td>
<td>&gt;1.3 ug/mL</td>
</tr>
<tr>
<td>Pneumo Ab Type 12 (12F)</td>
<td>&gt;1.3 ug/mL</td>
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<tr>
<td>Pneumo Ab Type 14</td>
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<tr>
<td>Pneumo Ab Type 19 (19F)</td>
<td>&gt;1.3 ug/mL</td>
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<td>Pneumo Ab Type 23 (23F)</td>
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<td>Pneumo Ab Type 26 (6B)</td>
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<tr>
<td>Pneumo Ab Type 51 (7F)</td>
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</tr>
<tr>
<td>Pneumo Ab Type 56 (18C)</td>
<td>&gt;1.3 ug/mL</td>
</tr>
</tbody>
</table>

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**Pneumocystis jiroveci, Molecular Detection, PCR, Varies**

**Clinical Information:** Pneumocystis pneumonia is an important cause of opportunistic infection in
immunocompromised patients, particularly those with HIV. The causative agent, Pneumocystis jiroveci, cannot be cultured in vitro and, therefore, laboratory detection has historically relied upon microscopic identification directly from patient specimens using fluorescent stains or antibodies. Unfortunately, stains often lack sensitivity and require expertise on the part of the reader in order to differentiate Pneumocystis jiroveci from staining artifacts and other fungi. This real-time PCR assay provides sensitive (21% more sensitive than direct detection using fluorescent calcofluor white stain), specific, and objective detection of Pneumocystis from bronchoalveolar lavage fluid and other specimens.

**Useful For:** Preferred test for detection of Pneumocystis

**Interpretation:** A positive result indicates the presence of Pneumocystis DNA. A negative result indicates the absence of detectable Pneumocystis DNA.

**Reference Values:**
Not applicable

**Clinical References:**

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**Podoplanin (D2-D40) Immunostain, Technical Component Only**

**Clinical Information:** Podoplanin (D2-40) is a mucin-type transmembrane glycoprotein that is expressed in reactive follicular dendritic cells (FDC), and its expression has been recently reported in FDC sarcomas. Podoplanin is expressed in a variety of other tissues, including lymphatic endothelium.

**Clinical References:**
bile duct cells, mesothelial cells, ependyma, myoepithelial cells, and granulosa cells. The D2-40 antibody to podoplanin has been used in the diagnosis of mesothelioma and seminoma.

**Useful For:** Aids in the identification of reactive follicular dendritic cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**FPOLO**

**Poliovirus (Types 1, 3) Antibodies, Neutralization**

**Clinical Information:** This sensitive procedure is recommended for vaccine response testing and type-specific serodiagnosis of recent poliovirus infection. It can also serve as an aid for diagnosing immune deficiency disorders.

**Reference Values:**
- Polio 1 Titer: <1:8
- Polio 3 Titer: <1:8

The presence of neutralizing serum antibodies (titers 1:8 up to >1:128) against polioviruses implies lifelong immunity. Some persons without detectable titers (<1:8) may also be immune as demonstrated by elicitation of a secondary-type serum antibody response upon rechallenge with live polio vaccine.

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**FPOLE**

**Pollock White (Pollachius virens) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10–0.34 Low Positive 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 High Positive 4 17.50–49.99 Very High Positive 5 50.00–99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
- <0.35 kU/L

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**PVJAK**

**Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis, Varies**

**Clinical Information:** The Janus kinase 2 (JAK2) gene codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. The JAK2 V617F is located in exon 14 and present in 50% to 60% of primary myelofibrosis and essential thrombocythemia, and 95% to 98%
of polycythemia vera (PV). In the rest of the polycythemia vera cases, over 50 different mutations have been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F JAK2 mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, some mutations may not be well characterized and requires further clinical and research evaluation.

**Useful For:** Aiding in the distinction between the myeloproliferative neoplasm polycythemia vera (PV) and other secondary erythrocytosis

**Interpretation:** The results will be reported as 1 of the 3 following states: - Positive for JAK2 V617F mutation - Positive for JAK2 mutation (other than V617F) - Negative for JAK2 mutations If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence are reported. A positive mutation status is highly suggestive of a myeloid neoplasm and may support a diagnosis of polycythemia vera in the appropriate clinical setting. Correlation with clinicopathologic findings and other laboratory results is necessary in all cases. A negative mutation status makes a diagnosis of polycythemia vera highly unlikely, although it does not completely exclude this possibility, other myeloproliferative neoplasms or other neoplasms.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Polyols, Quantitative, Urine**

**Clinical Information:** Polyols are sugar alcohols that have been identified in blood, urine, and cerebrospinal fluid. Characteristic patterns of abnormal polyols may suggest a disorder of the pentose phosphate pathway (PPP) including transaldolase (TALDO) deficiency and ribose-5-phosphate isomerase (RPI) deficiency. The PPP is involved in carbohydrate metabolism and is present in the cytosol of all cells. Two specific functions of the PPP are the production of nicotinamide adenine dinucleotide phosphate (NADPH) and the synthesis of ribose-5-phosphate, a molecule necessary for nucleotide and nucleic acid synthesis. Both TALDO and RPI deficiency that have multisystem involvement are recently described disorders of this pathway. TALDO deficiency is an autosomal recessive disorder caused by a reduction of the enzyme transaldolase. Clinical manifestations are characterized by severe neonatal liver failure, coagulopathy, low serum protein, hypoglycemia, high ammonia, progressive myocardial hypertrophy, and abnormal lactate dehydrogenase with remarkably normal or low transaminases. Patients may present in the antenatal period with maternal HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), hydrops fetalis and oligohydramnios, dysmorphic features, cutis laxa, and hypertrichosis. The clinical course is variable, but acute liver failure with normal transaminases is a common finding. Initially, hepatomegaly is absent, but the spleen may be enlarged. Later, hepatomegaly with liver cirrhosis and mild kidney failure occur. RPI deficiency is an autosomal recessive disorder caused by a deficiency of the enzyme ribose-5-phosphate isomerase. Clinical manifestations include neurological deficits such as slow progressing leukoencephalopathy and neuropathy. Additionally, spasticity, ataxia, epilepsy, regression, and delayed psychomotor development have been described. Polyols analysis in urine is the method of choice for the biochemical diagnosis of TALDO and RPI deficiency. Abnormal results should
be followed with either enzymatic or molecular genetic analysis.

**Useful For:** Diagnosis of transaldolase (TALDO) deficiency or ribose-5-phosphate isomerase (RPI) deficiency

**Interpretation:** An interpretive report will be provided. All profiles are reviewed by the laboratory director and interpretation is based on pattern recognition. A detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Erythritol</th>
<th>Arabinitol</th>
<th>Ribitol</th>
<th>Sedoheptulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 months</td>
<td>1-3 years</td>
<td>4-17 years</td>
<td>&gt; or =18 years</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed in mmol/mol creatinine

**Clinical References:**

**FPOM 57918**

**Pomegranate (Punica granatum) IgE**

**Interpretation:** Class IgE (kU/L) Comment
- 0 <0.35 Below Detection
- 0.35 – 0.69 Low Positive
- 0.70 – 3.49 Moderate Positive
- 3.50 – 17.49 Positive
- 17.50 – 49.99 Strong Positive
- 50.00 – 99.99 Very Strong Positive
- >99.99 Very Strong Positive

**Reference Values:**
- <0.35 kU/L

**PDCRF 606122**

**Pompe Disease Cross-Reactive Immunological Material Status, Fibroblasts**

**Clinical Information:** Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to alterations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen is taken up by lysosomes during physiologic cell turnover and accumulates, causing lysosomal swelling and cell damage, which results in organ dysfunction. Symptoms include progressive muscle weakness, cardiomyopathy, and, eventually, death if untreated. Clinically, Pompe disease is categorized into infantile and late-onset forms based on age of onset, organ involvement, and rate of progression. The infantile form (or classic Pompe disease) is the most severe variant and is characterized by early onset and rapid progression of cardiac, liver, and muscle problems resulting in death within the first year of life. The infantile variant of Pompe disease has a similar age of...
onset but a milder clinical presentation. Late-onset Pompe disease can present with muscle weakness, cardiomyopathy, and/or respiratory dysfunction in childhood or later, including advanced adulthood. The rate of progression and severity of symptoms is variable, particularly in the late-onset forms. Treatment with enzyme replacement therapy (ERT) is available, making early diagnosis of Pompe disease desirable because early initiation of treatment improves the prognosis. Treatment with ERT can prolong survival in patients with infantile onset Pompe disease; however, the effectiveness of treatment is impacted by the presence or absence of cross-reactive immunologic material (CRIM) to the GAA enzyme. Patients who are CRIM-negative are more likely to develop antibodies against recombinant human GAA than patients who are CRIM-positive, thereby decreasing the effectiveness of treatment. Strategies to decrease the immune response to ERT, such as immunosuppression, rely on determination of CRIM status. Molecular analysis of the GAA gene can determine CRIM status in over 90% of patients with Pompe disease (GAAZ / Pompe Disease, Full Gene Analysis, Varies). However, for those who have GAA variants that are not classified as either CRIM-negative or -positive, CRIM testing in fibroblasts or leukocytes can determine final CRIM status. Therefore, CRIM testing is useful for either confirmation of CRIM status determined by molecular testing or determination of CRIM status if the genotype is not informative.

**Useful For:** Determination of cross-reactive immunologic material status in patients with Pompe disease Evaluating the best strategy for enzyme replacement therapy for patients with Pompe disease

**Interpretation:** The presence of cross-reactive immunologic material (CRIM) indicates a decreased likelihood that a patient affected with Pompe disease (acid alpha-glucosidase: GAA deficiency) will develop an immune response to enzyme replacement therapy with recombinant GAA. The absence of CRIM in untreated patients with Pompe disease indicates a need to consider additional measures to prevent an immune response to the administration of enzyme replacement therapy with recombinant GAA.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**
cardiomyopathy, and/or respiratory dysfunction in childhood or later, including advanced adulthood. The rate of progression and severity of symptoms is variable, particularly in the late-onset forms. Treatment with enzyme replacement therapy (ERT) is available, making early diagnosis of Pompe disease desirable because early initiation of treatment improves the prognosis. Treatment with ERT can prolong survival in patients with infantile onset Pompe disease; however, the effectiveness of treatment is impacted by the presence or absence of cross-reactive immunologic material (CRIM) to the GAA enzyme. Patients who are CRIM-negative are more likely to develop antibodies against recombinant human GAA than patients who are CRIM-positive, thereby decreasing the effectiveness of treatment. Strategies to decrease the immune response to ERT, such as immunosuppression, rely on determination of CRIM status. Molecular analysis of the GAA gene can determine CRIM status in over 90% of patients with Pompe disease (GAAZ / Pompe Disease Full Gene Analysis, Varies). However, for those who have GAA variants that are not classified as either CRIM-negative or -positive, CRIM testing in leukocytes can determine final CRIM status. Therefore, CRIM testing is useful for either confirmation of CRIM status determined by molecular testing or determination of CRIM status if the genotype is not informative.

**Useful For:** Determination of cross-reactive immunologic material status using leukocytes from patients with Pompe disease Evaluating the best strategy for enzyme replacement therapy for patients with Pompe disease

**Interpretation:** The presence of cross-reactive immunologic material (CRIM) indicates a decreased likelihood that a patient affected with Pompe disease (acid alpha-glucosidase: GAA deficiency) will develop an immune response to enzyme replacement therapy with recombinant GAA. The absence of CRIM in untreated patients with Pompe disease indicates a need to consider additional measures to prevent an immune response to the administration of enzyme replacement therapy with recombinant GAA.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**
early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis.

Newborn screening can identify patients with all forms of Pompe disease, even before onset of symptoms. Unaffected patients with GAA pseudodeficiency alleles and carriers may also be identified by newborn screening. The ratio calculated between the creatine (Cre):creatinine (Crn) ratio as the numerator and the activity of GAA as the denominator can differentiate true cases of infantile and late-onset Pompe disease from false-positive cases (such as carriers and pseudodeficiency of GAA enzyme). When applied to the newborn screening setting, this second-tier testing can provide results in a timely fashion and provide better guidance in the decision to submit samples for further confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis, Varies).

**Useful For:** Second-tier testing of newborns with an abnormal primary screening result/decreased acid alpha-glucosidase enzyme for Pompe disease Follow-up testing for evaluation of an abnormal newborn screening result for Pompe disease

**Interpretation:** An interpretive report will be provided. The quantitative measurements of informative metabolites and related ratios are evaluated using the Collaborative Laboratory Integrated Reports (CLIR) system. The report is in text form only, indicating if the applicable ratio is normal or abnormal and whether or not the CLIR postanalytical tool is informative for Pompe disease. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics. Recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) are provided in the interpretative report.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Pompe Disease, Blood Spot**

**Clinical Information:** Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, eventually, death. Patients with Pompe disease, especially those with infantile, childhood, and juvenile onset, can have elevations of serum enzymes (such as creatine kinase) secondary to cellular dysfunction. Delayed diagnosis of symptomatic patients with later onset Pompe disease is not unusual due to nonspecific and overlapping presentation (such as proximal muscle weakness and respiratory insufficiency) with more common neuromuscular diseases. The clinical phenotype of Pompe disease lies on a spectrum, with differing clinical phenotypes dependent on age of onset and residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life when left untreated. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Treatment with enzyme replacement therapy is available, making prompt diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. The ratio calculated between the creatine (Cre):creatinine (Crn) ratio as the numerator and the activity of GAA as the denominator can differentiate true cases of infantile and late-onset Pompe disease from false-positive cases such as carriers and pseudodeficiency of GAA enzyme. This determination can be performed in a timely fashion and provide better guidance in the decision to submit samples for further confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis).
Useful For: Evaluation of patients with a clinical presentation suggestive of Pompe disease (muscle hypotonia, weakness, or cardiomyopathy) outside of the newborn screening setting

Interpretation: An interpretive report (including acid alpha-glucosidase (GAA) activity and [Creatine/Creatinine]/GAA ratio, if applicable) is provided. The quantitative measurements of informative metabolites and related ratios are evaluated using the Collaborative Laboratory Integrated Reports (CLIR) system. The report is in text form only, indicating if the applicable ratio is normal or abnormal and whether or not the CLIR postanalytical tool is informative for Pompe disease. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics. Recommendations for additional biochemical testing and confirmatory studies (enzyme assay, biomarker testing, molecular analysis) are provided in the interpretative report.

Reference Values:
An interpretive report will be provided.


GAAZ 35430

Pompe Disease, Full Gene Analysis, Varies

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive condition caused by deficiency of acid alpha-glucosidase. Enzyme insufficiency results in symptoms such as muscle weakness, cardiomyopathy, and respiratory problems. Pathogenic alterations in the GAA gene (which encodes acid alpha-glucosidase) are associated with Pompe disease. The diagnosis of this heterogeneous condition relies on both clinical and laboratory evaluation. Clinically, the condition is categorized into infantile and late-onset forms based on age of onset, organ involvement, and rate of progression. The infantile form (or classic Pompe disease) is the most severe form and is characterized by early onset and rapid progression of cardiac, liver, and muscle problems resulting in death within the first year. The infantile variant form has a similar age of onset but a milder clinical presentation. On the less severe end of the spectrum is the late-onset form with childhood, juvenile, or adult onset. The rate of progression and severity of symptoms is quite variable, particularly in the late-onset forms. The incidence varies by clinical type and ethnic population; the combined incidence is approximately 1 in 40,000 individuals. The calculated ratio of creatine (Cre) and creatinine (Crn) to acid-alpha glucosidase (GAA) activity is useful for individuals with a suspected diagnosis of Pompe disease; for patients older than 6 weeks, order PDBS / Pompe Disease, Blood Spot; for patients 6 weeks and younger, order PD2T / Pompe Disease Second-Tier Newborn Screening, Blood Spot. Alternatively, enzyme studies can be ordered on blood via GAAW / Acid Alpha-Glucosidase, Leukocytes. When clinical manifestations and results of that analysis are supportive of a diagnosis of Pompe disease, variant analysis of the GAA gene is warranted. Additionally, measurement of the urine glucotetrasaccharide biomarker can aid in diagnosis and ongoing therapeutic monitoring (HEX4 / Glucotetrasaccharides, Random, Urine) Over 250 different variants have been identified in this gene including point alterations and large deletions. GAA full gene sequencing provided by this test will detect 2 variants in approximately 83% to 93% of individuals with confirmed GAA enzyme deficiency. Identification of genetic variants provides confirmation of the diagnosis and allows for subsequent testing of at risk family members.

Useful For: Confirmation of diagnosis of Pompe disease (as a follow-up to biochemical analyses)

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

**Clinical References:**

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**FPOPW**

**Poplar White (Populus alba) IgE**

**Interpretation:**
- Class IgE (kU/L) Comment
  - 0 <0.35 Below Detection
  - 1 0.35 – 0.69 Low Positive
  - 2 0.70 – 3.49 Moderate Positive
  - 3 3.50 – 17.49 Positive
  - 4 17.50 – 49.99 Strong Positive
  - 5 50.00 – 99.99 Very Strong Positive
  - 6 >99.99 Very Strong Positive

**Reference Values:**
- <0.35 kU/L

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**POPSD**

**Poppy Seed, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:**
- Establishing the diagnosis of an allergy to poppy seed
- Defining the allergen responsible for eliciting signs and symptoms
- Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>
2 0.70-3.49  Positive
3 3.50-17.4  Positive
4 17.5-49.9  Strongly positive
5 50.0-99.9  Strongly positive
6 > or =100  Strongly positive Reference values apply to all ages.


FPORG
57627  Pork IgG
Interpretation:
Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FPRK4
57564  Pork IgG4
Interpretation:
Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

PORK
82700  Pork, IgE, Serum
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pork Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the
specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Porphobilinogen and Aminolevulinic Acid, Plasma**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and the excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, of the 5 hepatic porphyrias, 4 typically present with acute neurological manifestations and are designated the acute porphyrias. Clinically, however, these attacks can be prolonged and chronic. Three primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP but may be present in HCP and VP. Plasma porphobilinogen (PBG) and aminolevulinic acid (ALA) are elevated during the acute phase of these neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to distinguish among AIP, HCP, and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity (PBGD / Porphobilinogen Deaminase, Whole Blood). VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces). Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available for AIP (HMBSZ / HMBS Gene, Full Gene Analysis, Varies), HCP (CPOXZ / CPOX Gene, Full Gene Analysis, Varies), or VP (PPOXZ / PPOX Gene, Full Gene Analysis, Varies), which allows for diagnosis of at-risk family members. The very rare (<10 cases described) autosomal recessive aminolevulinic acid dehydratase deficiency porphyria (ADP) is also a primary acute porphyria causing neurovisceral symptoms with variable age of onset. Biochemically, ADP is characterized by an isolated significant elevation of aminolevulinic acid (ALA). More commonly, however, isolated elevations of ALA are due to secondary inhibition of ALA dehydratase with acute lead intoxication results in the highest degree of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication and tyrosinemia type I. The workup of patients with a suspected porphyria is most effective when following a stepwise
The following algorithms are available in Special Instructions or call 800-533-1710 to discuss testing strategies:

- Porphyria (Acute) Testing Algorithm
- Porphyria (Cutaneous) Testing Algorithm

Useful For: An equivalent option to urine for first-line test for evaluation of a suspected acute porphyria Monitoring patients undergoing treatment for an acute intermittent porphyria or other acute porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
- Porphobilinogen: < or =0.5 nmol/mL
- Aminolevulinic Acid: < or =0.5 nmol/mL

Clinical References:

PBGDW Porphobilinogen Deaminase, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase (HMBS). Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with a deficiency variant in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of PBGD enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (HMBSZ / HMBS Gene, Full Gene Analysis, Varies) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For: Confirmation of a diagnosis of acute intermittent porphyria using washed erythrocyte specimens
**PBGD**

**Porphobilinogen Deaminase, Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase (HMBS). Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with a deficiency variant in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of PBGD enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (HMBSZ / HMBS Gene, Full Gene Analysis, Varies) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Confirmation of a diagnosis of acute intermittent porphyria (AIP)

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available.

**Reference Values:** Reference ranges have not been established for patients who are <16 years of age.

<table>
<thead>
<tr>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 7.0 nmol/L/sec</td>
<td>&gt; or =7.0 nmol/L/sec</td>
</tr>
<tr>
<td>6.0-6.9 nmol/L/sec</td>
<td>6.0-6.9 nmol/L/sec (indeterminate)</td>
</tr>
<tr>
<td>&lt;6.0 nmol/L/sec</td>
<td>&lt;6.0 nmol/L/sec (diminished)</td>
</tr>
</tbody>
</table>

Porphyobilinogen, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfonamide drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP but may be present in HCP and VP. Urinary porphobilinogen (PBG) is elevated during the acute phase of the neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to distinguish between AIP, HCP and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity using PBGD_/Porphobilinogen Deaminase, Whole Blood. VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces). Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available, which allows for diagnosis of at-risk family members. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. The following algorithms are available in Special Instructions or call 800-533-1710 to discuss testing strategies: The following algorithms are available in Special Instructions or call 800-533-1710 to discuss testing strategies: -Porphyria (Acute) Testing Algorithm -Porphyria (Cutaneous) Testing Algorithm

Useful For: First-order test for evaluation of a suspected acute porphyria: acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

< or =1.3 mcmol/L

Porphyria Comprehensive Gene Panel, Varies

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as acute hepatic or chronic cutaneous, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Aminolevulinic acid dehydratase deficiency porphyria (ADP) is a rare, autosomal recessive porphyria that has a variable age at presentation. Clinical manifestations of acute porphyria include attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. A HCP and VP are also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Acute hepatic porphyrias are caused by autosomal dominant variants in 1 of 3 genes: HMBS, associated with AIP; CPOX, associated with HCP; and PPOX, associated with VP. Variants in these genes show incomplete penetrance, and patients with a confirmed deleterious variant may be asymptomatic. ADP is inherited in an autosomal recessive manner, due to two pathogenic variants in ALAD. The recommended first-tier tests to screen for acute hepatic porphyria are quantitative urinary porphyrins analysis (PQNRU / Porphyrins, Quantitative, Random, Urine) and fecal porphyrins analysis (FQPPS / Porphyrins, Feces) Cutaneous photosensitivity is associated with the chronic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyrinuria (EPP), X-linked protoporphyrinuria (XLP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies (sometimes referred to as erythropoietic uroporphyrinuria). PCT is the most common form of porphyria and is most commonly sporadic (acquired), but approximately 25% of cases are inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become cruste, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. The clinical presentation of EPP and XLP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Chronic porphyrias are caused by autosomal dominant pathogenic variants in UROD that are associated with inherited PCT or autosomal recessive variants in UROD that are associated with HEP. They are also due to autosomal recessive pathogenic variants in UROS or X-linked variants in GATA1 that are associated with CEP, or autosomal
recessive variants in FECH that are associated with EPP. In addition, autosomal dominant variants in CLPX, associated with EPP2, and X-linked variants in ALAS2, associated with XLP, are also causes of chronic porphyrias. A comprehensive gene panel is a helpful tool to establish a targeted diagnosis for patients with suggestive clinical and biochemical features of porphyria. The recommended first-tier biochemical testing for patients with a suspected porphyria is most effective when following a stepwise approach. For more information see Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions.

**Useful For:** Follow up for abnormal biochemical results suggestive of porphyria Establishing a molecular diagnosis for patients with porphyria Identifying variants within genes known to be associated with porphyria, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**PEWE 31893**

**Porphyrens Evaluation, Washed Erythrocytes**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by decreased ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. XLDPP is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fraction is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and free protoporphyrin are necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PEE / Porphyrins Evaluation, Whole Blood -PEWE / Porphyrins Evaluation, Washed Erythrocytes. The whole
blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Preferred test for analysis of erythrocyte porphyrins Establishing a biochemical diagnosis of erythropoietic protoporphyria, and X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:**
PORPHYRINS, TOTAL, RBC
<80 mcg/dL

**Clinical References:**

**Porphyrsins Evaluation, Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical, with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors can exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by decreased ferrochelatase activity resulting in significantly increased noncomplexed (free) protoporphyrin levels in erythrocytes, plasma, and feces. XLDPP is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fractionation is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and free protoporphyrin is necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PEE / Porphyrins Evaluation, Whole Blood -PEWE / Porphyrins Evaluation, Washed Erythrocytes. The whole blood option is easiest for
clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:**
PORPHYRINS, TOTAL, RBC
<80 mcg/dL

**Clinical References:**

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**Porphyrians, Feces**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrias and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms, which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly sporadic (acquired), but in about 25% of cases it is inherited in an autosomal dominant manner. The
most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) occurs when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Increased fecal porphyrin excretions are observed most commonly in symptomatic patients with CEP, PCT, HCP, and VP. In quiescent phases, as well as prior to puberty, fecal porphyrin excretion may be within normal limits. Patients with AIP may have elevated fecal porphyrin levels during severe attacks. EPP and XLDPP patients may have elevated protoporphyrin levels, however, these disorders cannot be diagnosed by fecal analysis alone. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:**
Evaluation of patients who present with signs or symptoms suggestive of porphyria cutanea tarda, hereditary coproporphyria, variegate porphyria, congenital erythropoietic porphyria, erythropoietic protoporphyria, or X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Porphyrin Type</th>
<th>Normal Range (mcg/24 hours)</th>
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<tr>
<td>Uroporphyrin I</td>
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</tr>
<tr>
<td>Uroporphyrin III</td>
<td>&lt;50</td>
</tr>
<tr>
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<tr>
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<td>&lt;20</td>
</tr>
<tr>
<td>Pentacarboxyl porphyrin III</td>
<td></td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
<20 mcg/24 hours

ISOPENTACARBOXYL PORPHYRINS
<80 mcg/24 hours

COPROPORPHYRIN I
<500 mcg/24 hours

COPROPORPHYRIN III
<400 mcg/24 hours

ISOCOPROPORPHYRIN
<200 mcg/24 hours

PROTOPORPHYRINS
<1,500 mcg/24 hours

COPROPORPHYRIN III/COPROPORPHYRIN I RATIO
<1.20

See The Heme Biosynthetic Pathway in Special Instructions.

**Clinical References:**

**Porphyrins, Quantitative, 24 Hour, Urine**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrrias. The porphyrrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrrias can be further classified as acute or chronic, based on their clinical presentation. The primary acute hepatic porphyrrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly
sporadic (acquired) but in about 25% of cases it is inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Urinary porphyrin determination is helpful in the diagnosis of most porphyrias including CEP, PCT, AIP, HCP, and VP. In addition, measurement of porphobilinogen (PBG) in urine is important in establishing the diagnosis of the acute neurologic porphyrias (AIP, HCP and VP). Neither urine porphyrins nor PBG is helpful in evaluating patients suspected of having EPP or XLDPP. In addition, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of uroporphyrin and/or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Preferred screening test for congenital erythropoietic porphyria and porphyria cutanea tarda and during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when specimen transport will be longer than 72 hours

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

**UROPORPHYRINS (OCTACARBOXYL)**

\(< \text{or} =30 \text{nmol/24 hours}\)

**HEPTACARBOXYLPORPHYRINS**

\(< \text{or} =9 \text{nmol/24 hours}\)

**HEXACARBOXYLPORPHYRINS**

\(< \text{or} =8 \text{nmol/24 hours}\)

**PENTACARBOXYLPORPHYRINS**

\(< \text{or} =10 \text{nmol/24 hours}\)

**COPROPORPHYRINS (TETRACARBOXYL)**

Males: \(< \text{or} =230 \text{nmol/24 hours}\)

Females: \(< \text{or} =168 \text{nmol/24 hours}\)

**PORPHOBILINOGEN**

\(< \text{or} =2.2 \text{mcmol/24 hours}\)

Porphyrrins, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrrias. The porphyrrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypopigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly sporadic (acquired) but in about 25% of cases it is inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypopigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatocerebrosporphyria porphyria (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. In addition, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrrias are characterized by increased excretion of, uroporphyrin and/or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For: Preferred test to begin assessment for congenital erythropoietic porphyria and porphyria cutanea tarda and during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when specimen transport will not exceed 72 hours

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach 1 of the laboratory directors in case the referring physician has additional questions.

Reference Values: UROPORPHYRINS, OCTA
< or =30 nmol/L

HEPTACARBOXYLPORPHYRINS
< or =7 nmol/L

HEXACARBOXYLPORPHYRINS
< or =2 nmol/L

PENTACARBOXYLPORPHYRINS
< or =5 nmol/L

COPROPORPHYRINS, TETRA
< or =110 nmol/L

PORPHOBILINOGEN
< or =1.3 mcmol/L


PTP 8731

Porphyrias, Total, Plasma

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. These enzyme defects cause various porphyrins and their precursors to accumulate in different specimen types. The detection and differentiation of the porphyrias is through evaluation of the patterns of porphyrin accumulation observed in erythrocytes and plasma and of the heme precursors excreted in urine and feces. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may occur in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyria, porphyria cutanea tarda (PCT), and the erythropoietic porphyrias including erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and can be either sporadic (acquired) or inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions; fluid filled vesicles that rupture easily become crusted and heal slowly, which result from mild trauma to sun-exposed areas. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and alopecia following repeated skin damage. Liver disease is common as evidenced by abnormal liver function tests, and 30% to 40% of
patients with PCT develop cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) occurs when an individual inherits a PCT-causing genetic variant from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Plasma porphyrins are most appropriate for monitoring treatment of PCT. Although analysis in plasma is not recommended for diagnosis, increases in plasma porphyrin concentrations are observed in the cutaneous porphyrias and may be elevated during acute episodes of AIP, VP, and HCP. In addition, persons in chronic renal failure who develop bullous dermatosis similar to that associated with PCT may have increased plasma porphyrins. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. The following algorithms are available in Special Instructions or call 800-533-1710 to discuss testing strategies:

-Porphyria (Acute) Testing Algorithm
-Porphyria (Cutaneous) Testing Algorithm

**Useful For:** Monitoring treatment of patients with porphyria cutanea tarda

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
< or =1.0 mcg/dL

**Clinical References:**

**POSA 89591**

**Posaconazole, Serum**

**Clinical Information:** Posaconazole interferes with fungal cytochrome P450 (CYP) lanosterol-14 alpha demethylase activity, decreasing synthesis of ergosterol, the principal sterol in fungal cell membrane, and inhibiting fungal cell membrane formation.(1,2) Posaconazole has been approved for prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients (eg, hematopoietic stem cell transplant recipients with graft-versus-host disease: GVHD or those with prolonged neutropenia secondary to chemotherapy for hematologic malignancies) and treatment of oropharyngeal candidiasis (including patients refractory to itraconazole or fluconazole).(1,3) It also is approved for ocular administration (drug monitoring not required for this use). Posaconazole has a variable absorption. Food and liquid nutritional supplements increase absorption and fasting states do not provide sufficient absorption to ensure adequate plasma concentrations.(4,5) The drug has a high volume of distribution (Vd=465-1,774 L) and is highly protein bound (> or =97%), predominantly bound to albumin.(1,3) The drug does not undergo significant metabolism; approximately 15% to 17% undergoes non-CYP-mediated metabolism, primarily via hepatic glucuronidation into metabolites.(1) The half-life elimination is approximately 35 hours (range: 20-66 hours); steady-state is achieved after about 5 to 7 days. Time to maximum concentration is approximately 3 to 5 hours but, due to the highly variable absorption, trough level monitoring is recommended. Therapeutic drug monitoring should be considered in the following situations: -To document optimal absorption when used for prophylaxis or active treatment of a fungal infection -Consider rechecking a level even if initial level was in the goal range if the patient: -Is unable to meet optimal nutritional intake -Is receiving continuous tube feeding -Is receiving a proton pump inhibitor (decreased posaconazole levels in some studies) -Has mucositis, diarrhea, vomiting, GVHD, or other reason that the drug may not be absorbed well
Useful For: Monitoring of posaconazole therapy

Interpretation: Levels greater than 700 ng/mL (0.7 mcg/mL) have been suggested for prophylaxis. Levels greater than or equal to 1250 ng/mL (1.25 mcg/mL) were shown to be optimal in a salvage trial for treatment of invasive Aspergillus infections. Toxic range has not been established.

Reference Values:
>700 ng/mL (trough)


Post Vasectomy Check, Semen

Clinical Information: Following a vasectomy, sperm may be found in the semen for 6 weeks to 3 months or longer. Regular ejaculation (every 3-4 days) may eliminate sperm from the reproductive tract more quickly. To check for the absence of sperm, semen should be evaluated for the presence of sperm 3 months postvasectomy and after a minimum of 20 ejaculations. Because the sperm count may be very low, the semen is centrifuged for concentration purposes. A negative result from 1 well-mixed postvasectomy semen specimen generally indicates that use of contraception is no longer necessary. Occasional cases have been reported where postvasectomy semen analysis (PVSA) shows intermittent presence of rare nonmotile sperm (RNMS) in the semen.(1)

Useful For: Determining absence or presence of sperm postvasectomy

Interpretation: Patients may stop using other methods of contraception when examination of 1 well-mixed postvasectomy semen specimen shows azoospermia or rare nonmotile sperm (RNMS < or = 100,000 nonmotile sperm/mL). The risk of pregnancy after vasectomy is approximately 1 in 2,000 for men who have postvasectomy azoospermia or postvasectomy semen analysis (PVSA) showing RNMS.(1) If >100,000 nonmotile sperm/mL persist beyond 6 months after vasectomy, then trends of serial PVSA and clinical judgment should be used to decide whether the vasectomy is a failure and whether repeat vasectomy should be considered.(1) Vasectomy should be considered a failure if any motile sperm are seen on PVSA at 6 months after vasectomy, in which case repeat vasectomy should be considered.

Reference Values:
Zero sperm seen


Postmortem Arrhythmia Panel, Varies

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (ages 15-35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. The reported incidence of SCD is likely an underestimate since more overt causes of death, such as car accidents and drownings, may result from arrhythmogenic events. In cases of sudden unexplained death where autopsy does not detect a structural basis for sudden death, a hereditary arrhythmia may be suspected. Brugada syndrome (BrS) and long QT syndrome (LQTS) are inherited forms of cardiac arrhythmia that may cause sudden cardiac death. Postmortem diagnosis of a hereditary arrhythmia may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members. BrS is a genetic cardiac disorder characterized by ST
segment elevation in leads V1-V3 on electrocardiography (EKG) with a high-risk for ventricular arrhythmias that can lead to sudden cardiac death. BrS is inherited in an autosomal dominant manner and is caused by pathogenic variants in genes that encode cardiac ion channels. The diagnosis of BrS is established based on the characteristic EKG abnormality along with personal and family health history, and also requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances. Genes associated with BrS include CACNA1C, CACNA2D1, GPD1L, KCNE3, KCNJ8, SCN3B, CACNB2, SCN1B, and SCN5A. Additional clinical information about BrS can be found in MCL’s BRGGP / Brugada Syndrome Multi-Gene Panel, Blood test.

LQTS is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on EKG, and may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. LQTS may also be associated with congenital profound bilateral sensorineural hearing loss, a condition known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either the KCNQ1 or KCNE1 genes. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the CACNA1C gene. Genes associated with LQTS include AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, and SNTA1. Additional clinical information about LQTS can be found in MCL’s ID LQTGP / Long QT Syndrome Multi-Gene Panel, Blood test.

**Useful For:** Providing a postmortem genetic evaluation in the setting of sudden unexplained death and suspicion for long QT or Brugada syndrome Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
of a hereditary cardiomyopathy may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members. The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathies are often caused by inherited, genetic, factors. When the identified structural or functional abnormality observed in a patient cannot be explained by acquired causes, genetic testing is commonly employed to identify a genetic underpinning. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). HCM is characterized by left ventricular hypertrophy in the absence of other causes, such as structural abnormalities, systemic hypertension, or physiologic hypertrophy due to rigorous athletic training (so-called "athlete’s heart"). The incidence of HCM in the general population is approximately 1 in 500, and is most often caused by variants in genes encoding the components of the cardiac sarcomere. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals who harbor pathogenic HCM-associated variants, but can cause life-threatening arrhythmias that increase the risk of sudden cardiac death in other individuals. DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias or conduction system disease, or thromboembolic disease (stroke). The incidence of DCM is likely higher than originally reported due to subclinical phenotypes and underdiagnosis, with recent estimates suggesting that DCM affects approximately 1 in every 250 people. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. Arrhythmogenic cardiomyopathy (also referred to as arrhythmogenic right ventricular cardiomyopathy/dyplasia) (ARVD or AC) is characterized by replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. Age of onset and severity are variable, but symptoms typically develop in adulthood. The incidence of AC is approximately 1 in 1,000 to 1 in 2,500. LVNC is characterized by left ventricular hypertrophy and prominent trabeculations of the ventricular wall, giving a spongy appearance to the muscle wall. It is thought to be caused by the arrest of normal myocardial morphogenesis. Clinical presentation is highly variable, ranging from no symptoms to congestive heart failure and life-threatening arrhythmias. An increased risk of thromboembolic events is also present with LVNC. Approximately 67% of LVNC is considered familial. Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy and is associated with abnormally rigid ventricular walls. Systolic function can be normal or near normal, but diastolic dysfunction is present. There are several nongenetic causes of RCM, but this condition can be familial as well, with the TNNT3 gene accounting for the majority of inherited cases. The age at presentation for familial RCM ranges from childhood to adulthood, and there is an increased risk of sudden death associated with this condition. Noonan syndrome is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, and characteristic facial dysmorphology. HCM is present in approximately 20% to 30% of individuals affected with Noonan syndrome. There are a number of disorders with significant phenotypic overlap with Noonan syndrome, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). Noonan syndrome and related disorders (also called the RASopathies) are caused by variants in genes involved in the RAS-MAPK signaling pathway. In some cases, variants in these genes may cause cardiomyopathy in the absence of other syndromic features. Cardiomyopathy may also be caused by an underlying disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder. In these cases, heart disease may be the first feature to come to attention clinically. The hereditary forms of cardiomyopathy are most frequently associated with an autosomal dominant form of inheritance, however X-linked and autosomal recessive forms of disease are also present. In some cases, compound heterozygous or homozygous variants may be present in genes typically associated with autosomal dominant inheritance, often leading to a more severe phenotype. Digenic variants (2 different heterozygous variants at separate genetic loci) in autosomal dominant genes have also been reported to occur in patients with severe disease (particularly HCM and ARVC). The inherited cardiomyopathies display both allelic and locus heterogeneity, whereby a single gene may cause different forms of cardiomyopathy (allelic heterogeneity) and variants in different genes can cause the same form of cardiomyopathy (locus heterogeneity). This comprehensive cardiomyopathy panel includes sequence analysis of 55 genes and may be considered for individuals with HCM, DCM, AC, or LVNC, whom have had uninformative test results from a more targeted, disease-specific test. This test may also be
helpful when the clinical diagnosis is not clear, or when there is more than 1 form of cardiomyopathy in the family history. It is important to note that the number of variants of uncertain significance detected by this panel may be higher than for the disease-specific panels, making clinical correlation more difficult. Genes included in the Postmortem Cardiomyopathy Panel Gene Protein Inheritance Disease Association ABC9 ATP-binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKR D1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM BRAF V-RAF murine sarcoma viral oncogene homolog B1 AD Noonan/CFC/Costello syndrome CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tayetayama-type distal myopathy, rippling muscle disease CBL CAS-BR-M murine ectropic retroviral transforming sequence homolog AD Noonan-like syndrome disorder CRYAB Crystallin, alpha-B AD, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, AC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD DSC2 Desmocollin AD, AR AC, ARVC + skin and hair findings DSG2 Desmoglein AD AC DSP Desmplakin AD, AR, DCM, Carvajal syndrome DTNA Dystrobrevin, alpha AD LVNC, CHD, GLA Galactosidase, alpha X-linked Fabry disease HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome JUP Junction plakoglobin AD, AR AC, NaXos disease KRAS V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/LAM A4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated member protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan-like syndrome with loose anagen hair SOS1 Son of sevenless, dropsophil, homolog 1 AD Noonan syndrome TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TCAP Titin-cap (telethonin) AD, AR DCM, TMEM43 Transmembrane protein 43 AD, EMD TNNC1 Troponin C AD, EMD TNNI3 Troponin I, cardiac AD, AR DCM, HCM, RCM TTN Tropomyosin 1 AD HCM, DCM, LVNC TTN Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR DCM, DCM, ARVC, myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emery muscular dystrophy (EMD), congenital heart defect (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

**Useful For:** Providing a comprehensive postmortem genetic evaluation in the setting of sudden unexplained death or with a personal or family history suggestive of hereditary cardiomyopathy Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions...
made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.


Postmortem Marfan and Related Panel, Varies

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (ages 15-35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden death, autopsy may identify a structural abnormality such as aortic aneurysm or dissection. Postmortem diagnosis of a hereditary form of aortic aneurysm/dissection may assist in confirmation of the cause of death, as well as risk assessment in living family members. Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue and occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and aortic root dilatation/dissection and mitral valve prolapse are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of FBN1. Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the FBN1 gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis). Loeyes-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by variants in TGFB1 and TGFB2. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for...
aneurysm and dissection throughout the arterial tree. Variants in the SMAD3 gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Thoracic aortic aneurysm and dissections (TAAD) is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is ACTA2, followed by TGFBR1 and TGFBR2, and MYH11. Variants in the MYLK gene have been reported in a small subset of families with familial TAAD. TGFBR2 variants have also been reported in families with TAAD and systemic features that overlap with LDS and MFS. The COL3A1 gene causes Ehlers Danlos syndrome type IV (vascular type), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously. Autosomal dominant variants of the FBN2 gene are known to cause congenital contractual arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm. Variants of the CBS gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting. Variants in the SKI gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS but, when present, it can be severe. Homozygous and compound heterozygous loss of function variants in the SLC2A10 gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features. Many of these described disorders have distinct genetic causes but may present phenotypically similarly, leading to difficulty in accurate diagnosis. However, gene-based management strategies have been described for some of these disorders. Therefore, comprehensive genetic analysis may be useful for accurate diagnosis and gene-based management. Genes included in Postmortem Marfan and Related Panel: Gene Protein Inheritance Known Association ACTA2 Actin, alpha-2, smooth muscle, aorta AD TAAD CBS Cystathionine beta-synthase AR Homocystinuria COL3A1 Collagen, type III, alpha-1 AD Ehlers-Danlos syndrome type IV (vascular type) FBN1 Fibrillin 1 AD Marfan syndrome/TAAD/ectopia lentis/ MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome FBN2 Fibrillin 2 AD Congenital contractual arachnodactyly MYH11 Myosin, heavy chain 11, smooth muscle AD TAAD MYLK Myosin light chain kinase AD TAAD SKI V-SKI avian sarcoma viral oncogene homolog AD Shprintzen-Goldberg syndrome SLC2A10 Solute carrier family 2 (facilitated glucose transporter), member 10 AR Arterial Tortuosity syndrome/TAAD (autosomal recessive) SMAD3 Mothers against decapentaplegic, drosophila, homolog of, 3 AD Loey-Dietz syndrome/TAAD TGFBR1 Transforming growth factor-beta receptor, type I AD Loey-Dietz syndrome/TAAD TGFBR2 Transforming growth factor-beta receptor, type II AD Loey-Dietz syndrome/TAAD Abbreviations: Autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to thoracic aortic dissection or with a personal or family history suggestive of Marfan syndrome, Loey-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder. Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

PMNSR 65562

Postmortem Noonan and Related Panel, Varies

Clinical Information: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity whose characteristic features can include short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. In approximately 20% to 30% of cases, Noonan syndrome and related disorders are associated with hypertrophic cardiomyopathy, which may lead to sudden cardiac death. Postmortem diagnosis of Noonan syndrome or a related disorder may assist in confirmation of the cause of death, as well as risk assessment in living family members. Other heart defects associated with Noonan syndrome and related disorders include pulmonary valve stenosis (20%-50%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous variants in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a pathogenic variant in approximately 75% of affected individuals. NS can be sporadic and due to new (de novo) variants; however, an affected parent can be recognized in 30% to 75% of families. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 variants are more likely to be found when pulmonary stenosis is
present, while hypertrophic cardiomyopathy is commonly associated with RAF1 variants, but rarely associated with PTPN11. A number of related disorders exist that have phenotypic overlap with NS and are caused by variants in the same group of genes. PTPN11 and RAF1 variants have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Variants in BRAF, MAP2K1, MAP2K2, and KRAS have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with variants in HRAS. Variation in SHOC2 has been associated with a distinctive phenotype involving features of Noonan syndrome and loose anagen hair. Genes included in the Postmortem Noonan and Related Gene Protein Inheritance Disease Association BRAF V-RAF murine sarcoma viral oncogene homolog b1 AD Noonan/CFC/Costello syndrome CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan-like syndrome disorder HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome KRAS V-KI-RAS Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome MAP2K1 Mitogen-activated protein kinase, kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase, kinase 2 AD Noonan/CFC NRAS Neuroblastoma ras viral oncogene homolog AD Noonan syndrome PTPN11 Protein-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/LEOPARD syndrome RAF1 V-raf-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome SHOC2 Suppressor of clear, c. Elegans, homolog of AD Noonan-syndrome like with loose anagen hair SOS1 Son of sevenless, drosophila, homolog 1 AD Noonan-like syndrome with loose anagen hair Abbreviations: autosomal dominant (AD)

**Useful For:** Providing a comprehensive postmortem genetic evaluation in the setting of sudden cardiac death and suspicion for Noonan syndrome or related disorders Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:** An interpretive report will be provided.

Postmortem Screening, Bile and Blood Spot

Clinical Information: Postmortem screening involves acylcarnitine analysis in blood and bile specimens to evaluate cases of sudden or unexpected death. Acylcarnitine analysis can diagnose disorders of fatty acid oxidation and several organic acidurias, as well as some enzyme deficiencies that cause the accumulation of specific acyl-CoAs as measured by this assay. Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body’s supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry (MS/MS). Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method, including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor and vitamin supplementation. Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. Disorders Detectable by Acylcarnitine Analysis* Fatty Acid Oxidation Disorders: -Short-chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase (VLCA) deficiency -Carnitine palmitoyl transferase type II (CPT-II) deficiency -Carnitine-acylcarnitine translocase (CACT) deficiency -Electron-Transferring Flavoproteins (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency: MADD; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic Acidemia -Methylmalonic Acidemia -Isovaleric Acidemia -3-Hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -Beta-ketothiolase deficiency -Malonic aciduria -Etylmalonic encephalopathy *Further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than 1 condition. See Postmortem Screening Algorithm in Special Instructions.

Useful For: Postmortem evaluation of individuals at any age who died suddenly or unexpectedly; testing is particularly recommended under the following circumstances (risk factors): -Family history of sudden infant death syndrome or other sudden unexpected deaths at any age -Family history of Reye syndrome -Maternal complications of pregnancy (acute fatty liver pregnancy, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count]) -Lethargy, vomiting, fasting in the 48 hours prior to death -Allegation of child abuse (excluding obvious cases of trauma, physical harm) -Macrosopic findings at autopsy: - Fatty infiltration of the liver - Dilated or hypertrophic cardiomyopathy - Autopsy evidence of infection that routinely would not represent a life-threatening event

Interpretation: Reports of abnormal acylcarnitine profiles will include an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) as indicated, name and phone number of contacts who may provide these studies at Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not always sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) or molecular genetic
Analyses are required using additional tissue such as skin fibroblasts from the deceased patient. If not available, molecular genetic analysis of a patient's parents may enable the confirmation of a diagnosis.

**Reference Values:**
Quantitative results are compared to a constantly updated range which corresponds to the 5 to 95 percentile interval of all postmortem cases analyzed in our laboratory.

**Clinical References:**

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**Potassium, 24 Hour, Urine**

**Clinical Information:** Potassium (K+) is the major intracellular cation. Functions of potassium include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires the body to maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular concentration is 20 times greater than the extracellular K+ concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute kidney disease and end-stage kidney failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of non-potassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

**Useful For:** Determining the cause for hyper- or hypokalemia

**Interpretation:** Hypokalemia reflecting true total body deficits of potassium (K+) can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is below 30 mEq/day, it can be concluded that renal reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of more than 30 mEq/d in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.

**Reference Values:**
> or =18 years: 16-105 mmol/24 hours

Reference values have not been established for patients who are <18 years of age.

**Clinical References:**

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**Potassium, Random, Urine**

**Clinical Information:** Potassium (K+) is the major intracellular cation. Functions of K+ include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires the body to maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular K+ concentration is 20 times greater than the extracellular concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in

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both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute kidney disease and end-stage kidney failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of non-potassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

**Useful For:** Determining the cause for hyper- or hypokalemia using a random urine specimen

**Interpretation:** Hypokalemia reflecting true total body deficits of potassium (K+) can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is less than 30 mEq/day, it can be concluded that renal reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of more than 30 mEq/day in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.

**Reference Values:**
No established reference values
Random urine potassium may be interpreted in conjunction with serum potassium, using both values to calculate fractional excretion of potassium.

The calculation for fractional excretion (FE) of potassium (K) is

\[
FE(K) = \left(\frac{[K\text{ (urine)} \times \text{ Creat}\text{(serum)}}}{[K\text{ (serum)} \times \text{ Creat}\text{(urine)}}]\right) \times 100
\]

**Clinical References:**

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**Potassium, Serum**

**Clinical Information:** Potassium is the major cation of the intracellular fluid. Disturbance of potassium homeostasis has serious consequences. Decreases in extracellular potassium are characterized by muscle weakness, irritability, and eventual paralysis. Cardiac effects include tachycardia, other cardiac conduction abnormalities that are apparent by electrocardiographic examination, and eventual cardiac arrest. Hypokalemia (low potassium) is common in vomiting, diarrhea, alcoholism, and folic acid deficiency. Additionally, more than 90% of hypertensive patients with aldosteronism have hypokalemia. Abnormally high extracellular potassium levels produce symptoms of mental confusion; weakness, numbness, and tingling of the extremities; weakness of the respiratory muscles; flaccid paralysis of the extremities; slowed heart rate; and eventually peripheral vascular collapse and cardiac arrest. Hyperkalemia may be seen in end-stage renal failure, hemolysis, trauma, Addison disease, metabolic acidosis, acute starvation, dehydration, and with rapid potassium infusion. Potassium should be monitored during treatment of many conditions but especially in diabetic ketoacidosis and any intravenous therapy for fluid replacement.

**Useful For:** Evaluation of electrolyte balance, cardiac arrhythmia, muscular weakness, hepatic encephalopathy, and renal failure

**Interpretation:** Potassium levels below 3.0 mmol/L are associated with marked neuromuscular symptoms and are evidence of a critical degree of intracellular depletion. Potassium levels below 2.5 mmol/L are potentially life-threatening. High potassium can be an acute medical emergency, particularly if the potassium increases over a short period of time. At values above 6.0 mmol/L, symptoms are typically apparent. Potassium levels above 6.0 mmol/L are potentially lifethreatening. Levels above 10.0 mmol/L are, in most cases, fatal.

**Reference Values:**
<1 year: not established
> or =1 year: 3.6-5.2 mmol/L

**Clinical References:** Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER
Poultry and Meat Panel IgG

**Interpretation:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PPOX Gene, Full Gene Analysis, Varies

**Clinical Information:** Variegate porphyria (VP) is an autosomal dominant (AD) cutaneous porphyria that can present with/or without acute attacks that phenocopy acute intermittent porphyria (AIP). The most common clinical presentation of VP is increased photosensitivity, blistering, hyperpigmentation, and skin fragility in sun-exposed areas. The acute attacks of VP can include abdominal pain, vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. Cutaneous manifestations include edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases patients present with isolated photosensitivity. Variegate porphyria is caused by mutations in the PPOX gene. Mutations are typically inherited in an autosomal dominant fashion with incomplete penetrance, although homozygous mutations have been reported in association with a more severe clinical phenotype in early childhood. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in distinguishing variegate porphyria from AIP and hereditary coproporphyria.

**Useful For:** Confirmation of variegate porphyria for patients with clinical and biochemical features of the disease. Identification of familial PPOX mutation to allow for genetic testing in family members.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Prader-Willi/Angelman Syndrome, Molecular Analysis, Varies

**Clinical Information:** Prader-Willi syndrome (PWS) is a congenital disorder characterized by a biphasic clinical course. Neonates with PWS are hypotonic, have a weak cry, and are poor feeders, but improve over time. In later infancy and childhood, individuals with PWS have global developmental delay, short stature, hypogonadism, small hands and feet, and marked hyperphagia leading to obesity.
PWS is thought to be due to loss of function of paternally expressed genes, although specific genes have not yet been definitively implicated in the phenotype of PWS. Etiology of Prader-Willi syndrome:

- Chromosome 15 deletion (15q11-13): approximately 70%-75%
- Maternal uniparental disomy (UPD): 20%-30%
- Imprinting defect: 1%-5%
- Chromosome rearrangement: rare

The phenotype caused by paternal deletions of 15q11-13 and by maternal UPD are generally identical with the exception of relative hypopigmentation being more common in patients with deletion PWS. Angelman syndrome (AS) is a nonprogressive congenital disorder characterized by more significant developmental delay and mental retardation, ataxia, seizures, jerky arm movements, macrostomia, tongue thrusting, unprovoked laughter, brachycephaly, and virtual absence of speech. AS is due to loss of function of the maternally expressed gene UBE3A. Etiology of Angelman syndrome:

- Chromosome 15 deletion (15q11-13): approximately 70%-75%
- Paternal UPD: approximately 5%
- UBE3A mutation: approximately 10%
- Imprinting defect: 2%-5%
- Chromosome rearrangement: rare
- Unknown: approximately 10%

The phenotype of AS patients with maternal deletions is generally more severe than that associated with paternal UPD or imprinting defects, including a higher rate or severity of microcephaly, seizures, and motor difficulties. Patients with AS caused by paternal UPD or imprinting defects generally show better growth and higher developmental and language abilities. Both chromosome 15 deletions and UPD most often occur as de novo events during conception and, thus, recurrence risk to siblings is very low. In rare cases, chromosome 15 deletions and UPD occur as a result of parental translocations or other rare cytogenetic rearrangements, and in these cases recurrence risks to siblings are increased. The recurrence risk associated with imprinting defects is dependent on whether or not there is an identifiable mutation. UBE3A mutations can occur sporadically or be inherited in an autosomal dominant fashion. There is a 50% recurrence risk to siblings in cases of an inherited UBE3A mutation. Due to the complex genetic etiology of PWS and AS and the corresponding variability in recurrence risks, careful cytogenetic and molecular testing and family assessment are necessary to provide accurate genetic counseling. Initial studies to rule-out PWS or AS should include chromosomal microarray analysis to identify chromosome abnormalities that may have phenotypic overlap with PWS or AS, and methylation-sensitive multiple ligation-dependent probe amplification (MLPA) to identify deletions, duplications, and methylation defects. In cases where methylation-sensitive MLPA suggests either deletion or duplication, FISH can be used to confirm type I and type II deletions or characterize the disease mechanism, respectively. In cases where methylation-sensitive MLPA suggests abnormal methylation in the absence of a deletion or duplication, UPD studies can be used to characterize the disease mechanism. Assessment of patients found to have a deletion in the PWS/AS critical region on routine cytogenetic analysis or chromosomal microarray can include confirmation of the deletion by FISH analysis and MLPA analysis to define parent of origin. See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions for more information.

**Useful For:** Confirmation of diagnosis in patients suspected of having either Prader-Willi syndrome (PWS) or Angelman syndrome (AS) based on clinical assessment or previous laboratory analysis Prenatal diagnosis in families at risk for PWS or AS

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
thyroxine and retinol-binding protein. The serum concentration of prealbumin reflects the synthesis capacity of the liver and is markedly diminished in malnutrition and other conditions. Due to its short half-life of approximately 2 days, prealbumin can be used for monitoring the nutritional status and efficacy of parenteral nutrition.

**Useful For:** Assessing nutritional status, especially in monitoring the response to nutritional support in the acutely ill patient

**Interpretation:** Results below the reference intervals for adults and pediatric patients may suggest protein depletion. Clinical correlation recommended with patient status and other nutritional markers.

**Reference Values:**
< or =18 years: 12-32 mg/dL  
>18 years: 19-38 mg/dL


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**Pregabalin, Serum**

**Clinical Information:** Pregabalin (Lyrica) is an anticonvulsant drug used to treat partial seizures in patients and is a more potent successor to gabapentin. Pregabalin is commonly used for neuropathic pain and fibromyalgia. This test can be used by physicians to assess compliance and may be clinically useful in patients with renal failure who generally require lower dosages. Therapeutic and toxic ranges are not well defined. Therapeutic concentrations are reported to be from 2 to 5 mcg/mL, while toxicity may occur at concentrations above 10 mcg/mL.

**Useful For:** Monitoring serum pregabalin (Lyrica) concentrations, assessing compliance, and adjusting dosage in patients.

**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and other clinical tests. This may provide useful information in patients showing poor response, noncompliance, or adverse effects. Toxicity can occur with concentrations greater or equal to 10 mcg/mL.

**Reference Values:**
2.0-5.0 mcg/mL


---

**Pregnenolone and 17-Hydroxypregnenolone, Serum**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries,
testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxyprogrenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxyprogrenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxyprogrenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** An ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out. Confirming a diagnosis of 3-beta-hydroxy dehydrogenase (3-beta-HSD) deficiency and 17-alpha-hydroxylase deficiency. Analysis for 17-hydroxyprogrenolone is also useful as part of a battery of tests to evaluate females with hirsutism or infertility. Both can result from adult-onset CAH.

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be decreased; 17-hydroxyprogrenolone and pregnenolone and DHEA levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as seen in CYP21A2 mutation, and cortisol also is low, but 17-OHPG is only mildly, if at all, elevated. In the also very rare 17-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenolone, 17-OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-doxycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**

**PREGNENOLONE**

**CHILDREN***

**Males**

- 0-6 years: not established
- 7-9 years: <206 ng/dL
- 10-12 years: <152 ng/dL
- 13-15 years: 18-197 ng/dL
- 16-17 years: 17-228 ng/dL

**Tanner Stages**

- Stage I: <157 ng/dL
- Stage II: <144 ng/dL
- Stage III: <215 ng/dL
- Stage IV-V: 19-201 ng/dL

**Females**

- 0-6 years: not established
- 7-9 years: <151 ng/dL
- 10-12 years: 19-220 ng/dL
- 13-15 years: 22-210 ng/dL

Current as of June 14, 2021 12:13 pm CDT   800-533-1710 or 507-266-5700 or mayocliniclabs.com
16-17 years: 22-229 ng/dL
Tanner Stages
Stage I: <172 ng/dL
Stage II: 22-229 ng/dL
Stage III: 34-215 ng/dL
Stage IV-V: 26-235 ng/dL

ADULTS
> or =18 years: 33-248 ng/dL

17-HYDROXYPREGNENOLONE
CHILDREN*
Males
Premature (26-28 weeks): 1,219-9,799 ng/dL
Premature (29-36 weeks): 346-8,911 ng/dL
Full term (1-5 months): 229-3,104 ng/dL
6 months-364 days: 221-1,981 ng/dL
1-2 years: 35-712 ng/dL
3-6 years: <277 ng/dL
7-9 years: <188 ng/dL
10-12 years: <393 ng/dL
13-15 years: 35-465 ng/dL
16-17 years: 32-478 ng/dL
Tanner Stages
Stage I: <209 ng/dL
Stage II: <356 ng/dL
Stage III: <451 ng/dL
Stage IV-V: 35-478 ng/dL

Females
Premature (26-28 weeks): 1,219-9,799 ng/dL
Premature (29-36 weeks): 346-8,911 ng/dL
Full term (1-5 months): 229-3,104 ng/dL
6 months-364 days: 221-1,981 ng/dL
1-2 years: 35-712 ng/dL
3-6 years: <277 ng/dL
7-9 years: <213 ng/dL
10-12 years: <399 ng/dL
13-15 years: <408 ng/dL
16-17 years: <424 ng/dL
Tanner Stages
Stage I: <236 ng/dL
Stage II: <368 ng/dL
Stage III: <431 ng/dL
Stage IV-V: <413 ng/dL

ADULTS
Males
> or =18 years: 55-455 ng/dL
Females
> or =18 years: 31-455 ng/dL


**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** An ancillary test for congenital adrenal hyperplasia, particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase deficiency

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-Hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxypregnenolone and pregnenolone and dehydroepiandrosterone levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as seen in CYP21A2 mutation, and cortisol also is low, but 17-OHPG is only mildly, if at all, elevated. In the also very rare 17-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, 17-OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 2090
CHILDREN*

Males
0-6 years: not established
7-9 years: <206 ng/dL
10-12 years: <152 ng/dL
13-15 years: 18-197 ng/dL
16-17 years: 17-228 ng/dL

Tanner Stages
Stage I: <157 ng/dL
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Females
0-6 years: not established
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10-12 years: 19-220 ng/dL
13-15 years: 22-220 ng/dL
16-17 years: 22-229 ng/dL

Tanner Stages
Stage I: <172 ng/dL
Stage II: 22-229 ng/dL
Stage III: 34-215 ng/dL
Stage IV-V: 26-235 ng/dL

ADULTS
> or =18 years: 33-248 ng/dL


Prenatal Aneuploidy Detection, FISH

Clinical Information: Approximately half of clinically recognizable spontaneous abortions have a major chromosomal anomaly. Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8/1,000 have a major chromosome anomaly, of which 6.5/1,000 involve aneuploidy of the 5 chromosomes analyzed by this test. Therefore, aneuploidy of chromosomes 13, 18, 21, X, and Y accounts for 81% to 95% of major chromosome anomalies in liveborn infants. Techniques to detect aneuploidy include standard chromosome analysis and FISH. Standard chromosome analysis from amniotic fluid cells or chorionic villi requires 5 to 9 days for culture, harvest, and analysis. FISH, which uses DNA probes and can be performed on cultured and uncultured cells, can rapidly detect aneuploidy of 13, 18, 21, X, and Y in uncultured amniotic fluid cells or chorionic villi. FISH-based analysis may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes.
**Useful For:** Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in prenatal specimens

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Prenatal Hepatitis Evaluation, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic; others may develop chronic liver disease including cirrhosis and hepatocellular carcinoma. HBV is spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles by drug addicts). The virus is found in virtually every type of human body fluid and also is spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy.

**Useful For:** Screening pregnant women for chronic hepatitis B Determining the level of infectivity of chronic hepatitis B in pregnant women This test is not useful for diagnosis of hepatitis B during the "window period" of acute hepatitis B virus infection (ie, after disappearance of hepatitis B surface antigen and prior to appearance of hepatitis B surface antibody).

**Interpretation:** Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. A confirmed positive result for HBsAg is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Hepatitis Be-antigen (HBeAg) appears at approximately the same time as HBsAg and indicates that the virus is replicating and the individual is infectious. Appearance of hepatitis Be antibody (anti-HBe) after the disappearance of HBsAg and HBeAg usually indicates recovery and loss of infectivity.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**
# Previous Hepatitis (Unknown Type), Serum

**Clinical Information:** Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of the viral hepatitis in United States adults. HAV infection is spread by the oral/fecal route and produces acute hepatitis that follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and in institutions or high density centers such as prisons and health care centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these chronic carriers are asymptomatic, others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Viral Hepatitis Serologic Profiles

**Useful For:** Determining if an individual has been infected following exposure to an unknown type of hepatitis Obtaining baseline serologic markers of an individual exposed to a source with an unknown type of hepatitis Determining immunity to hepatitis A and B viral infections

**Interpretation:** Hepatitis A: Antibody against hepatitis A antigen (anti-HAV) is almost always detectable by the onset of symptoms (usually 15-45 days after exposure). The initial antibody consists almost entirely of the IgM subclass of antibody. Anti-HAV IgM usually falls to undetectable levels 3 to 6 months after infection. Anti-HAV IgG levels rise quickly once the virus is cleared and persist for many years. Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. Hepatitis C: Hepatitis C virus antibody (anti-HCV) is usually not detectable during the early months following infection, but is almost always detectable by the late convalescent stage of infection. Anti-HCV is not neutralizing and does not provide immunity.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPATITIS B SURFACE ANTIGEN</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>HEPATITIS B SURFACE ANTIGEN CONFIRMATION</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Surface Antibody</td>
<td></td>
</tr>
<tr>
<td>Unvaccinated: negative</td>
<td></td>
</tr>
<tr>
<td>Vaccinated: positive</td>
<td></td>
</tr>
</tbody>
</table>
Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <5.0 mIU/mL
Vaccinated: > or =12.0 mIU/mL

HEPATITIS B CORE TOTAL ANTIBODIES
Negative

HEPATITIS A IgG ANTIBODY
Unvaccinated: negative
Vaccinated: positive

HEPATITIS C ANTIBODY
Negative

HEPATITIS C VIRUS RNA DETECTION and QUANTIFICATION by REAL-TIME RT-PCR
Undetected

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.


**Primingone and Phenobarbital, Serum**

Clinical Information: Primidone is used for control of grand mal seizures that are refractory to other antiepileptics and seizures of psychomotor or focal origin. Primidone is initially dosed in progressively increasing amounts starting with 100 mg at bedtime to 250 mg 3 times a day after 10 days of therapy in adults. Primidone exhibits a volume of distribution of 0.6 L/kg and a half-life of 8 hours. When monitoring primidone and phenobarbital levels simultaneously, the specimen should be drawn just before the next dose is administered. Primidone is not highly protein bound, approximately 10%. Phenobarbital is a metabolite of primidone. Like phenobarbital, there are no known major drug-drug interactions that affect the pharmacology of primidone. Toxicity associated with primidone is primarily due to the accumulation of phenobarbital. Diagnosis and treatment are as described for PBAR / Phenobarbital, Serum.

Useful For: Assessing compliance Monitoring for appropriate therapeutic levels of primidone and phenobarbital Assessing toxicity

Interpretation: At steady-state, which is achieved approximately 2 weeks after therapy is initiated,
blood levels of primidone that correlate with optimal response to the drug range from 9.0 to 12.5 mcg/mL for adults and 7.0 to 10.0 mcg/mL for children <5 years of age. The corresponding levels for phenobarbital are 20.0 to 40.0 mcg/mL for adults and 15.0 to 30.0 mcg/mL for children <5 years of age. Dosage adjustment based on blood level information is the best way to obtain optimal response to the drug.

**Reference Values:**

**Primidone**
- Therapeutic: 5.0-12.0 mcg/mL
- Critical value: > or = 15.0 mcg/mL

**Phenobarbital**
- Therapeutic: 10.0-40.0 mcg/mL
- Critical value: > or = 60.0 mcg/mL


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**Privet Tree, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to privet tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

apply to all ages.
PRKAR1A Full Gene Sequencing and Deletion/Duplication Analysis, Varies

Clinical Information: Carney complex (CNC) is an autosomal dominant disorder caused by heterozygous germline pathogenic inactivating variants in the PRKAR1A gene. This condition has also been designated by the following acronyms: NAME (nevi, atrial myxomas, ephelides) and LAMB (lentigines, atrial myxoma, blue nevi). CNC is characterized by skin pigmentation abnormalities, myxomas, endocrine tumors, and schwannomas. The most common presenting feature of CNC is unusual skin pigmentation, including brown skin spots called lentigines or blue-black moles called blue nevi. Myxomas are noncancerous (benign) tumors which can occur in the heart (cardiac myxoma), skin, breast, and other internal organs. Cardiac myxomas can occur at a young age, and may block blood flow through the heart, causing serious complications or sudden death. Approximately 25% of affected individuals will develop primary pigmented nodular adrenocortical disease (PPNAD), which can lead to development of Cushing syndrome. Large-cell calcifying Sertoli cell tumors occur in most affected males and may develop in the first decade of life in about one third of cases. Multiple thyroid nodules are present in as many as 75% of affected individuals. Pituitary adenomas resulting in clinically evident acromegaly occur in approximately 10% of adults with CNC. Another 10% of affected individuals have psammomatous melanotic schwannomas, which are typically benign but may be malignant. PRKAR1A encodes for cAMP-dependent protein kinase type I-alpha regulatory subunit. PRKAR1A functions as a canonical tumor-suppressor gene, with biallelic inactivation in tumors resulting in constitutive activation of protein kinase A (PKA). Approximately 70% of individuals with a diagnosis of CNC have an affected parent, while approximately 30% have a de novo pathogenic variant. CNC is a highly penetrant disorder, with approximately 95% of those with a pathogenic PRKAR1A variant developing disease by age 50 years. The proportion of probands with a pathogenic variant detectable by sequence analysis is approximately 60%, but can be higher (approximately 80%) in individuals presenting with Cushing syndrome caused by PPNAD. Approximately 10% to 20% of individuals with CNC who test negative for a pathogenic sequence variant may have a large PRKAR1A deletion. While the majority of reported pathogenic PRKAR1A gene variants are associated with CNC, this gene is also associated with an autosomal dominant condition called acrodysostosis-1 with hormone resistance. This condition is characterized by multiple hormone resistance, short stature, brachycephaly, and short broad hands with short metacarpals and phalanges, among other features. This phenotype results from pathogenic PRKAR1A variants in 1 of the 2 cAMP-binding domains and has a different mechanism of disease than CNC.

Useful For: Aiding in the diagnosis of individuals with suspected Carney complex Aiding in the diagnosis of individuals with suspected acrodysostosis-1 with hormone resistance

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


GAL2 606833

Probability of Hepatocellular Carcinoma, Serum

Clinical Information: Biomarkers of hepatocellular carcinoma (HCC) include alpha fetoprotein (AFP), third electrophoretic form of lentil lectin-reactive AFP (AFP-L3), and des-carboxy-prothrombin (DCP). The GALAD model combines these three biomarkers with the patient’s gender and age to estimate the probability of HCC in patients with chronic liver disease based on the following equation: $Z = -10.08 + 0.09 \times \text{age} + 1.67 \times \text{sex} + 2.34 \log(10) \times \text{AFP} + 0.04 \times \text{AFP-L3} + 1.33 \times \log(10) \times \text{DCP}$, where sex = 1 for males, 0 for females. The probability estimate of HCC is calculated as follows: $Pr(\text{HCC}) = \frac{\exp(Z)}{1 + \exp[Z]}$. The GALAD model has been demonstrated to have higher diagnostic accuracy for the detection of HCC when compared to the use AFP, AFP-L3, and DCP markers alone or in combination. The performance of the GALAD score has also been reported to be superior to ultrasound for HCC detection.

Useful For: Calculation of the probability for patients with chronic liver disease to develop hepatocellular carcinoma

Interpretation: The probability of the presence of hepatocellular carcinoma (HCC) is estimated from the GALAD model score. Higher GALAD model scores correlate with increased risk of HCC. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve of the GALAD score was 0.95 for all HCC detection, and 0.92 for the detection of early stage HCC. Additionally, the AUC of the GALAD score (0.95) was higher than that of ultrasound alone for all HCC detection (AUC of 0.82, P <0.01). The sensitivity and specificity performance characteristics of the GALAD score for HCC will be influenced by the selected GALAD score cut-off. For example at an optimal AUC cutoff of 0.76, the GALAD score had 91% sensitivity and 85% specificity for HCC detection. At a more specific GALAD score cutoff of 0.88, the observed sensitivity was 80% for HCC detection with an observed specificity of 97%. The GALAD model was developed and validated in patient cohorts with a prevalence of HCC ranging from 35% to 49%. The performance of the model may be altered in populations with different HCC prevalence. In addition, the clinical performance of the GALAD score varies by etiology of HCC and therefore may be different in different regions of the world.

Reference Values:
Only orderable as part of a profile. For more information see HCCGS / Hepatocellular Carcinoma Risk Panel with GALAD Score, Serum

Not applicable

**Procainamide and N-Acetylprocainamide, Serum**

**Clinical Information:** Procainamide (PA) is indicated in the treatment of life-threatening ventricular arrhythmias. PA is metabolized to an active metabolite, N-acetylprocainamide (NAPA), with metabolism controlled by genetically determined enzymes. In patients with normal renal function, fast metabolizers will have a PA:NAPA ratio less than 1 at 3 hours after the dose is administered. Slow acetylators (PA:NAPA ratio >2 after 3 hours) are more likely to present with systemic lupus erythematosus-like symptoms and may test positive for antinuclear antibodies. Patients who have prolonged exposure to procainamide levels above 12 mcg/mL or a NAPA concentration of 40.0 mcg/mL or higher are very likely to exhibit symptoms of toxicity, which are characterized by hypotension, ventricular fibrillation, widened QRS complex, junctional tachycardia, oliguria, confusion, nausea, and vomiting. Renal disease, hepatic disease, cardiac failure, and states of low cardiac output reduce the metabolism and clearance of PA and NAPA. Coadministration of histamine H2 receptor antagonists, such as cimetidine and ranitidine reduce renal clearance of PA and NAPA resulting in higher plasma concentrations of each.

**Useful For:** Monitoring therapy with procainamide Assessing compliance Evaluating procainamide toxicity

**Interpretation:** Administration of a dose of 50 mg/kg will usually yield the optimal trough concentration in the range of 4.0 to 10.0 mcg/mL for procainamide and 12.0 to 18.0 mcg/mL for N-acetylprocainamide.

**Reference Values:**

- **Procainamide**
  - Therapeutic: 4.0-10.0 mcg/mL
  - Critical value: >12.0 mcg/mL

- **N-acetylprocainamide**
  - Therapeutic: 12.0-18.0 mcg/mL
  - Critical value: > or =40.0 mcg/mL


**Procalcitonin, Serum**

**Clinical Information:** Procalcitonin (ProCT) is a 116-amino acid precursor of calcitonin (CT). ProCT is processed to an N-terminal 57 amino acid peptide (CT [32-amino acids] and a 21-amino acid C-terminal peptide, catacalcin [CCP-1]). Expression of this group of peptides is normally limited to thyroid C cells and, to a small extent, other neuroendocrine cells. CT is the only hormonally active of...
these peptides. CT is secreted by C cells in response to hypercalcemia and inhibits bone resorption by osteoclasts, minimizing oscillations in serum calcium and calcium loss. During severe systemic inflammation, in particular related to bacterial infection, the tissue-specific control of CT-related peptides expression breaks down and ProCT and CCP-1 (referred collectively to as ProCT) are secreted in large quantities by many tissues. CT levels do not change. Noninfectious inflammatory stimuli need to be extremely severe to result in ProCT elevations, making it a more specific marker for severe infections than most other inflammatory markers (cytokines, interleukins, and acute-phase reactants). ProCT elevations are also more sustained than those of most other markers and occur in neutropenic patients. This reduces the risk of false-negative results. ProCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours. ProCT secretion parallels closely the severity of the inflammatory insult, with higher levels associated with more severe disease and declining levels with resolution of illness. In the absence of an ongoing stimulus, ProCT is eliminated with a half-life of 24 to 35 hours, making it suitable for serial monitoring. Finally, the dependence of sustained ProCT elevations on ongoing inflammatory stimuli allows identification of secondary septic events in conditions that can result in noninfectious ProCT elevations, such as cardiac surgery, severe trauma, severe burns, and multiorgan failure. ProCT levels should fall at a predictable pace in the absence of secondary infection.

**Useful For:** Diagnosis of bacteremia and septicemia in adults and children (including neonates) Diagnosis of renal involvement in urinary tract infection in children Diagnosis of bacterial infection in neutropenic patients Diagnosis, risk stratification, and monitoring of septic shock Diagnosis of systemic secondary infection post-surgery, and in severe trauma, burns, and multiorgan failure Differential diagnosis of bacterial versus viral meningitis Differential diagnosis of community-acquired bacterial versus viral pneumonia Monitoring of therapeutic response to antibacterial therapy

**Interpretation:** General considerations: In children older than 72 hours and in adults, levels below 0.15 ng/mL make a diagnosis of significant bacterial infection unlikely. Procalcitonin (ProCT) between 0.15 and 2.0 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. Levels above 2.0 ng/mL are highly suggestive of systemic bacterial infection/sepsis or severe localized bacterial infection, such as severe pneumonia, meningitis, or peritonitis. They can also occur after severe noninfectious inflammatory stimuli such as major burns, severe trauma, acute multiorgan failure, or major abdominal or cardiothoracic surgery. In cases of noninfectious elevations, ProCT levels should begin to fall after 24 to 48 hours. Autoimmune diseases, chronic inflammatory processes, viral infections, and mild localized bacterial infections rarely lead to elevations of ProCT of more than 0.5 ng/mL. Specific diagnostic applications, based on the current consensus in the literature: Diagnosis of bacteremia in neonates: After birth ProCT values increase from birth to reach peak values at about 24 hours of life and the decrease gradually by 48 hours of life. Therefore, during the first 72 hours of life different reference ranges will apply to newborn infants at different hours of age. ProCT levels on newborns suffering from early sepsis are significantly higher than those of noninfected newborns when reference ranges by hours of age are used. (1,2) Adult levels should apply at 72 hours or more after birth. Diagnosis of renal involvement in pediatric urinary tract infections: In children with urinary tract infections, a ProCT level above 0.5 ng/mL has 70% to 90% sensitivity and 80% to 90% specificity for renal involvement. ProCT responses in neutropenic patients are similar to patients with normal neutrophil counts and function, and the cutoffs discussed under general considerations above should be used. In the appropriate clinical setting, ProCT levels above 2.0 ng/mL on the first day of admission to the intensive care unit (ICU) represent a high risk for progression to severe sepsis and/or septic shock. ProCT levels below 0.5 ng/mL on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock. Reported sensitivity and specificity for the diagnosis of sepsis range from 60% to 100%, depending on underlying and coexisting diseases and the patient populations studied. The higher the ProCT level the worse the prognosis. A ProCT level below 0.5 ng/mL makes bacterial meningitis very unlikely. Most patients with bacterial meningitis will have ProCT levels of more than 10 times this level. With successful antibiotic therapy, ProCT levels should fall with a half-life to 24 to 35 hours.

**Reference Values:**
- Adults and children $\geq 72$ hours: $< 0.15$ ng/mL
- Children $< 72$ hours: $< 2.0$ ng/mL at birth, rises to $< 20$ ng/mL at 18-30 hours of age, then falls to $< 0.15$ ng/mL by 72 hours of age

**Clinical References:** 1. Chiesa C, Panero A, Rossi N, et al: Reliability of procalcitonin

**PINP**

**Procollagen I Intact N-Terminal, Serum**

**Clinical Information:** Procollagen type I propeptides are derived from collagen type I, which is the most common collagen type found in mineralized bone. In bone, collagen is synthesized by osteoblasts in the form of procollagen. This precursor contains a short signal sequence and terminal extension peptides: amino-terminal propeptide (PINP) and carboxy-terminal propeptide. These propeptide extensions are removed by specific proteinases before the collagen molecules form. Both propeptides can be found in the circulation and their concentration reflects the synthesis rate of collagen type I. Although collagen type I propeptides may also arise from other tissues (such as the skin, vessels, fibrocartilage, and tendons), most nonskeletal tissues exhibit a slower turnover than bone, and contribute very little to the circulating pool of PINP. PINP is considered the most sensitive marker of bone formation and it is particularly useful for monitoring bone formation therapies and antiresorptive therapies; it is recommended that the test be performed at baseline before starting osteoporosis therapy and performed again 3 to 6 months later.

**Useful For:** Aiding in monitoring antiresorptive and anabolic therapy in patients with osteoporosis An adjunct in the assessment of conditions associated with increased bone turnover such as Paget disease This test should not be used as a screening test for osteoporosis in the general population.

**Interpretation:** This test should be performed before beginning osteoporosis treatment (ie, prior to the start of therapy) to establish a baseline procollagen type I intact N-terminal propeptide (PINP) level. Three to 6 months after initiation of therapy, a change of 21% or more (least significant change) from baseline PINP levels indicates an adequate therapeutic response. This assay is specific for the intact trimeric form of PINP. The direction of the change in PINP levels (decrease or increase) will depend on the type of osteoporosis treatment. In patients taking bisphosphonates, PINP levels have been shown to decrease up to 70% from baseline after 6 months of therapy. Treatment with hormone replacement therapy also shows a decrease in PINP levels, but to a lesser degree than bisphosphonates therapy. In patients treated with teriparatide (recombinant human parathyroid hormone 1-34), PINP levels increase from baseline reflecting the stimulatory effect of teriparatide on osteoblasts and bone formation. PINP levels have been shown to significantly increase as early as 1 month after teriparatide treatment, peaking at 6 months following treatment. Increases of >10 mcg/L have been reported in 77% to 79% of teriparatide-treated patients after 3 months of therapy and are considered a successful response.

**Reference Values:**

Reference values have not been established for patients who are <18 years of age.

**Adult male:** 22-87 mcg/L

**Adult female premenopausal:** 19-83 mcg/L

**Adult female postmenopausal:** 16-96 mcg/L

Clinical Information: Venous thromboembolism (VTE) can describe: 1) a deep vein thrombosis (DVT), characterized by leg pain or tenderness typically in only one thigh or calf, leg swelling, skin that feels warm to the touch, and reddish discoloration or streaks, or 2) a pulmonary embolism (PE), characterized by unexplained shortness of breath, rapid breathing, chest pain under the rib cage, fast heart rate, and light headedness or passing out. VTEs affect about an estimated 900,000 individuals in the US per year.(2) While most individuals who experience a VTE do so only once in their life, some individuals may experience recurrent thrombotic episodes or have close relatives who do. The tendency to thrombose, sometimes referred to as thrombophilia or hypercoagulability, is considered a multifactorial disorder with many different factors increasing the risk for abnormal clotting. Thrombophilia is more likely to happen in people who are older, obese or overweight, and have conditions that promote blood coagulation like cancer or lupus. Other causes of acquired (non-genetic) thrombophilia include recent surgery, trauma, fractures, hospital or nursing home confinement, varicose veins, neurological disease with leg paresis, chronic renal disease, oral contraceptive use and hormone therapy, pregnancy and the post-partum period.(2) Less commonly, certain alterations in genes involved in blood coagulation may also increase the risk for thrombosis. A genetic cause for increased VTE may be considered in situations where a VTE occurs before the age of 40, is recurrent, occurs in multiple closely-related family members, and occurs in unusual locations in the body such as the portal, hepatic, mesenteric, or cerebral veins. Â The PROCR gene encodes for endothelial cell protein C receptor (EPCR), a transmembrane protein that plays a crucial role in the negative regulation of blood coagulation by increasing protein C activation five- to 20 fold via the thrombin-thrombomodulin complex.(3) Activated protein C (APC) then down regulates thrombin generation by inactivating factor VIIIa and factor Va.Â Rare alterations in the PROCR gene may increase the risk of thrombosis, especially in carriers of other prothrombotic alterations, by an unknown amount. As a whole, the PROCR gene and alterations in it are not well characterized and thus genetic testing has limited clinical utility. As of January 2019, only 3 missense alterations and a single nucleotide polymorphism (SNP) in the 5′UTR untranslated region (5′UTR) in PROCR are reported to be associated with increased risk for venous thromboembolism in the Human Gene Mutation Database (HGMD Professional 2018.4). The prevalence of individuals with pathogenic alterations in the PROCR gene in the general population or among individuals with VTE is unknown.

Useful For: Ascertaining a pathogenic alteration in the PROCR gene in patients with recurrent unprovoked venous thromboembolism (VTE)before the age of 40, a strong family history of unexplained and unprovoked VTE, and prior genetic testing for more common genetic variants associated with thrombophilia that does not correlate with the severity of the patientâ€™s thrombophilia or clinical presentation This test is not intended for prenatal diagnosis

Interpretation: An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Reference Values:
An interpretative report will be provided


**PROG**

**70542**

**Progesterone Receptor (PR) Immunostain, Technical Component Only**

**Clinical Information:** Progesterone receptor is a hormone receptor localized within the nucleus. It is highly expressed in the epithelial cells of the breast and endometrium, and smooth muscle cells of the uterus. This antibody is used along with that for estrogen receptor to assess hormonal responsiveness in breast cancer.

**Useful For:** Qualitative detection of progesterone receptor protein in a diagnostic setting

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**PGSN**

**8141**

**Progesterone, Serum**

**Clinical Information:** Sources of progesterone are the adrenal glands, corpus luteum, and placenta. Adrenal Glands: Progesterone synthesized in the adrenal glands is converted to other corticosteroids and androgens and, thus, is not a major contributor to circulating serum levels unless there is a progesterone-producing tumor present. Corpus Luteum: After ovulation, there is a significant rise in serum levels as the corpus luteum begins to produce progesterone in increasing amounts. This causes changes in the uterus, preparing it for implantation of a fertilized egg. If implantation occurs, the trophoblast begins to secrete human chorionic gonadotropin, which maintains the corpus luteum and its secretion of progesterone. If there is no implantation, the corpus luteum degenerates and circulating progesterone levels decrease rapidly, reaching follicular phase levels about 4 days before the next menstrual period. Placenta: By the end of the first trimester, the placenta becomes the primary secretor of progesterone.

**Useful For:** Ascertaining whether ovulation occurred in a menstrual cycle Assessment of infertility Evaluation of abnormal uterine bleeding Evaluation of placental health in high-risk pregnancy Determining the effectiveness of progesterone injections when administered to women to help support early pregnancy Workup of some patients with adrenal disorders

**Interpretation:** Ovulation results in a midcycle surge of luteinizing hormone (LH) followed by an increase in progesterone secretion, peaking between day 21 and 23. If no fertilization and implantation has
occurred by then, supplying the corpus luteum with human chorionic gonadotropin-driven growth stimulus, progesterone secretion falls, ultimately triggering menstruation. Typically, day 21 to 23 serum progesterone concentrations of more than 10 ng/mL indicate normal ovulation and concentrations below 10 ng/mL suggest anovulation, inadequate luteal phase progesterone production, or inappropriate timing of sample collection. Increased progesterone concentrations are occasionally seen with some ovarian cysts, molar pregnancies, rare forms of ovarian cancer, adrenal cancer, congenital adrenal hyperplasia, and testicular tumors. Increased progesterone may also be a result of overproduction by the adrenal glands. Low concentrations of progesterone may be associated with toxemia in late pregnancy, decreased ovarian function, amenorrhea, ectopic pregnancy, and miscarriage.

**Reference Values:**

Males:
- <4 weeks: Not established
- 4 weeks-<12 months: < or =0.66 ng/mL (confidence interval 0.63-0.94 ng/mL)
- 12 months-9 years: < or =0.35 ng/mL
- 10-17 years: Concentrations increase through adolescence and puberty
- 12 months-9 years: < or =0.35 ng/mL
- > or = 18 years (central 90th %): <0.20 ng/mL
- > or = 18 years: <0.20 ng/mL (Reference intervals are central 90th % of healthy population)

Females:
- <4 days old: Not established
- 4 days-12 months: < or =1.3 ng/mL (confidence interval 0.88-2.3 ng/mL)
- 12 months-9 years: < or =0.35 ng/mL
- 10-17 years: Adult concentrations are attained by puberty
- 12 months-9 years: < or =0.35 ng/mL
- Adult (central 90th %):
  - Follicular phase: < or =0.89 ng/mL
  - Ovulation: < or =12 ng/mL
  - Luteal phase: 1.8-24 ng/mL
  - Pregnancy
    - 1st trimester: 11-44 ng/mL
    - 2nd trimester: 25-83 ng/mL
    - 3rd trimester: 58-214 ng/mL
  - > or = 18 years:
    - Follicular phase: < or =0.89 ng/mL
    - Ovulation: < or =12 ng/mL
    - Luteal phase: 1.8-24 ng/mL
    - Post-menopausal: < or =0.20 ng/mL
    - Pregnancy
      - 1st trimester: 11-44 ng/mL
      - 2nd trimester: 25-83 ng/mL
      - 3rd trimester: 58-214 ng/mL

Pediatric reference intervals adopted from the CALIPER study.

www.sickkids.ca/caliperproject/index.html The Hospital for Sick Children. Toronto, Canada.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html


www.sickkids.ca/caliperproject/index.html
**Programmed Death-Ligand 1 (PD-L1) (22C3), Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

**Useful For:** Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone 22C3)

**Interpretation:** The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

**Clinical References:**

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**Programmed Death-Ligand 1 (PD-L1) (SP142), Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

**Useful For:** Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP142)

**Interpretation:** The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

**Clinical References:**

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**Programmed Death-Ligand 1 (PD-L1) (SP263), Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

**Useful For:** Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP263)

**Interpretation:** The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

**Clinical References:**
Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

Useful For: Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP263)

Interpretation: The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.


Progranulin Gene (GRN), Full Gene Analysis, Varies

Clinical Information: Frontotemporal lobar degeneration (FTLD) describes a group of neurodegenerative diseases that are frequent causes of dementia, accounting for 5% to 10% of all dementia patients and 10% to 20% of patients with onset of dementia before age 65. Frontotemporal dementia (FTD) is the most common clinical manifestation of FTLD. The clinical presentation of FTD is variable, but typically includes changes in personality and social conduct, often associated with impulse disinhibition, followed by more general cognitive decline, eventually leading to dementia. The age of onset is extremely variable ranging from 35 to 87 years. Duration of the disease ranges from 3 to 12 years. Based on the immunohistochemical staining, there are 2 main subtypes of FTLD: tau-positive FTLD and tau-negative FTLD with ubiquitin-positive inclusions (FTLD-U). Mutations in the MAPT gene have been identified in patients with tau-positive FTLD; mutations in the progranulin gene (GRN) have been identified in patients with FTLD-U. Both MAPT and GRN are located on chromosome 17q21, with GRN located only 1.7 Mb centromeric of MAPT. GRN consists of 12 coding and 1 noncoding exons. GRN encodes progranulin, a multifunctional protein that plays a role in multiple processes including development, wound repair, and inflammation. The function of GRN in the brain is not well understood, but progranulin is widely expressed in neurons and glial cells. More than 40 different pathogenic GRN mutations have been reported. All pathogenic mutations identified to date create functional null alleles that result in decreased progranulin production, suggesting that reduced levels of progranulin may lead to neurodegeneration.

Useful For: Aiding the diagnosis of frontotemporal dementia Distinguishing frontotemporal dementia from other dementias, including Alzheimer dementia Identifying individuals who are at increased risk of frontotemporal dementia

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Proinsulin, Plasma

**Clinical Information:** Proinsulin is the precursor of insulin and C-peptide (connecting peptide). Following synthesis, proinsulin is packaged into secretory granules, where it is processed to C-peptide and insulin by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E. Only 1% to 3% of proinsulin is secreted intact. However, because proinsulin has a longer half-life than insulin, circulating proinsulin concentrations are in the range of 5% to 30% of circulating insulin concentrations on a molar basis, with the higher relative proportions seen after meals and in patients with insulin resistance or early type 2 diabetes. Proinsulin can bind to the insulin receptor and exhibits 5% to 10% of the metabolic activity of insulin. Proinsulin levels might be elevated in patients with insulin-producing islet cell tumors (insulinomas). These patients suffer from hypoglycemic attacks due to inappropriate secretion of insulin by the tumors. The biochemical diagnosis rests primarily on demonstrating non-suppressed insulin levels in the presence of hypoglycemia (blood glucose <45 mg/dL). The diagnosis can be difficult, as tumors might be small or secrete insulin only episodically. Insulin injections or hypoglycemic drugs can also mimic insulinoma. Evaluation of these patients frequently requires a prolonged fast (72 hours), as well as supplementary tests in addition to insulin and glucose measurements, including a sulfonylurea screen, and measurement of C-peptide, proinsulin, and beta-hydroxybutyrate. The inappropriate oversecretion of insulin by insulinomas causes the release of an increased numbers of secretory granules with incompletely processed insulin, resulting in elevated serum/plasma proinsulin concentrations. This oversecretion of proinsulin in insulinomas is accentuated during fasting, when proinsulin normally does not account for more than 5% of the insulin concentrations. Proinsulin is strikingly elevated in PC1/3 deficiency. These patients have defects in the processing of multiple peptide hormones and suffer from diabetes, adrenal insufficiency, infertility, and obesity. Affected individuals typically have red hair regardless of racial background. Variants in the proinsulin molecule have been reported that affect PC cleavage efficiency or subsequent proinsulin metabolism. These variants can also lead to markedly elevated proinsulin levels, but are usually not accompanied by diabetes, or any other hormonal abnormalities.

**Useful For:** As part of the diagnostic workup of suspected insulinoma As part of the diagnostic workup of patients with suspected prohormone convertases1/3 deficiency As part of the diagnostic workup of patients with suspected proinsulin variations

**Interpretation:** Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (22 pmol/L) when hypoglycemic (blood glucose <60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range. The sensitivity and specificity for a diagnosis of insulinoma during hypoglycemia are approximately 75% and near 100%, respectively, at the 22 pmol/L cutoff. A higher sensitivity (>95%) can be achieved using a 5 pmol/L cutoff, and this is the cutoff recommended by Mayo Clinic's highly experienced hypoglycemia team to avoid missing cases. However, the lower cutoff results in a reduced specificity (approximately 40%), emphasizing the need for a combination of different tests to assure accurate biochemical diagnosis. Patients with PC1/3 deficiency have low, or sometimes undetectable, insulin levels and substantially elevated proinsulin levels, exceeding the upper limit of the reference range substantially in the fasting state and rising even higher after food intake. Many other hormonal abnormalities are also present, including cortisol deficiency (because of lack of processing of pro-opiomelanocortin to adrenocorticotropic hormone and other peptides), infertility, and, often, obesity.

**Reference Values:**

3.6-22 pmol/L

PRLI

Prolactin (PRL) Immunostain, Technical Component Only

Clinical Information: Prolactin is a pituitary hormone involved in the stimulation of milk production, salt and water regulation, growth, development, and reproduction. Prolactin-producing cells constitute approximately 20% of the cells of the normal anterior pituitary. Antibodies to prolactin are used in a panel to subclassify pituitary adenomas. Useful For: Subclassification of pituitary adenomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


PLPMA

Prolactin, Pituitary Macroadenoma, Serum

Clinical Information: Prolactin-secreting macroadenomas (>10 mm in diameter) can sometimes produce exceedingly high serum prolactin concentrations that may paradoxically result in falsely low prolactin concentrations when measured by immunometric assays. In such situations, very high concentrations of prolactin saturate both the capture and signal antibodies in the assay, block formation of the capture antibody-prolactin-signal antibody "sandwich," and result in falsely decreased prolactin results (referred to as the high-dose hook effect). With such tumors, serum prolactin levels may be falsely decreased into the normal reference interval, potentially resulting in inappropriate patient management. Dilution of the specimen eliminates the analytic artifact in these cases. Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and are also elevated during pregnancy, lactation, postpartum, and in the newborn infant. Hyperprolactinemia is the most common hypothalamic-pituitary...
disorder encountered in clinical endocrinology. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent in females than males, and accounts for approximately 40% of all pituitary tumors), functional and organic disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. In general, serum prolactin concentrations parallel tumor size in patients with prolactinomas. Macroadenomas (>10 mm in diameter) are typically associated with serum prolactin concentrations >250 ng/mL and a concentration >500 ng/mL is diagnostic of a macroadenoma. Moderately increased concentrations of serum prolactin are not a reliable guide for determining whether a prolactin-producing pituitary adenoma is present. Multiple medications can cause increased prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide, domperidone), alpha-methyldopa, cimetidine, opiates, antihypertensive medications, and other antidepressants and antipsychotics. Hyperprolactinemia often results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal females; and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

**Useful For:** Quantifying prolactin in serum specimens where the high-dose hook effect is suspected (eg, presence of pituitary tumor with symptoms of prolactinoma, and lower than expected serum prolactin concentration)

**Interpretation:** If no high-dose hook effect is observed, the following report comment will be included with the prolactin result: 10-, 100-, and 400-fold dilutions produced results consistent with the absence of high-dose hook effect. Total prolactin was measured using the Roche Cobas e immunoassay analyzer. If a high-dose hook effect is observed, which is demonstrated by significantly increasing concentrations of prolactin obtained after dilution of the serum, an interpretive comment will be included with the prolactin result. The Roche Cobas Prolactin II assay should demonstrate no high-dose hook effect at prolactin concentrations up to approximately 12,500 ng/mL.

**Reference Values:**

**Males**

- <18 years: not established
- > or =18 years: 4.0-15.2 ng/mL

**Females**

- <18 years: not established
- > or =18 years: 4.8-23.3 ng/mL

**Clinical References:**


**PRL**

**Prolactin, Serum**

**Clinical Information:** Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and concentrations are also elevated.
during pregnancy, lactation, postpartum, and in a newborn infant. Hyperprolactinemia is the most
common hypothalamic-pituitary disorder encountered in clinical endocrinology. Pathologic causes of
hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent
in females than males and accounts for approximately 40% of all pituitary tumors), functional and organic
disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall
lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. Hyperprolactinemia often
results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal
females, and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and
premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis.
Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function
and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are
often present. The treatment options are the same as in adult patients.

**Useful For:** Aiding in evaluation of pituitary tumors, amenorrhea, galactorrhea, infertility, and
hypogonadism Monitoring therapy of prolactin-producing tumors

**Interpretation:** In general, serum prolactin concentrations parallel tumor size in patients with
prolactinomas. Macroadenomas (>10 mm in diameter) are typically associated with serum prolactin
concentrations above 250 ng/mL, and a concentration above 500 ng/mL is diagnostic of a
macroprolactinoma. Moderately increased concentrations of serum prolactin are not a reliable guide for
determining whether a prolactin-producing pituitary adenoma is present. After initiation of medical
therapy of prolactinomas, prolactin levels should decrease substantially in most patients; in 60% to 80% of
patients, normal levels should be reached. Failure to suppress prolactin levels may indicate tumors
resistant to the usual central-acting dopamine agonist therapies; however, a subset of patients will show
tumor shrinkage despite persistent hyperprolactinemia. Patients who show neither a decrease in
prolactin levels nor tumor shrinkage might require additional therapeutic measures. In patients where a
discrepancy between pituitary tumor size and prolactin elevation is observed, a test for false-low serum
prolactin (hook effect) should be performed by serial dilution. See PLPMA / Prolactin, Pituitary
Macroadenoma, Serum. This assay should demonstrate no high-dose hook effect at prolactin
concentrations up to approximately 12,500 ng/mL.(1) Multiple medications can cause increased
prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine
antagonists (eg, metoclopramide, domperidone), alpha-methylidopa, cimetidine, opiates,
antihypertensive medications, and other antidepressants and antipsychotics. In patients with
asymptomatic hyperprolactinemia, assessment for macroprolactin (prolactin bound to immunoglobulin)
is suggested. Macroprolactin is detected by differing degrees depending on the immunoassay used to
measure prolactin. This assay shows low reactivity with most forms of macroprolactin. Macroprolactin
should be evaluated in asymptomatic hyperprolactinemic subjects or when pituitary imaging studies are
not informative. See MCRPL / Macroprolactin, Serum.

**Reference Values:**

**Males**

<18 years: not established

> or =18 years: 4.0-15.2 ng/mL

**Females:**

<18 years: not established

> or =18 years: 4.8-23.3 ng/mL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

**Clinical References:** 1. Package insert: Roche E170/cobas e601/e602 Prolactin II. Roche
DE, eds.Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. Elsevier Saunders
prolactin in two cases of invasive macroprolactinoma. Pituitary. 2002;5:261-265 4. Casaneuva FF,
Molitch ME, Schlecte JA, et al: Guidelines of the Pituitary Society for the diagnosis and management of
Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin
Endocrinol Metab. 2011 Feb;96(2):273-288
Prolonged Clot Time Profile Interpretation

Clinical Information: When coagulation screening tests are performed to verify normal function of the coagulation system (e.g., preoperative, routine examination), they sometimes indicate an abnormality that may be unexplained (i.e., prolonged clotting times). This consultation provides as comprehensive a workup as needed to define the abnormality and validation of the prolongation. Possibilities for a cause of prolongation include: -Artifactual due to high hematocrit (-dilution of specimen by anticoagulant if patient hematocrit is 55% or greater) -Factor deficiencies, congenital or acquired -Factor inhibitors e.g., factor VIII inhibitors (bleeding disorder) -Lupus anticoagulant (risk for thrombosis or recurrent miscarriage) -Anticoagulant drug effect including warfarin: Coumadin or Jantoven, oral anti-Xa inhibitors, oral direct thrombin inhibitors, and heparin.

Useful For: Determining the cause of prolongation of prothrombin time or activated partial thromboplastin time Screening for prolonged clotting times and determining the presence of factor deficiencies or inhibitor (e.g., factor-specific, lupus-like, or the presence of heparin)

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Prolyl Hydroxylase Domain-2 (PHD2/EGLN1) Gene Sequencing, Whole Blood

Clinical Information: Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by variants in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new alterations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing alterations is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal level to increased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal level to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Genetic variants resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are A heterozygous truncating variants. EPOR alterations are associated with decreased to normal EPO levels and normal p50 values (see Table).

Useful For: Assessing PHD2/EGLN1 in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: An interpretive report will be provided as a part of the HEMP / Hereditary Erythrocytosis Mutations, Whole Blood and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.
Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

An interpretive report will be provided.


FPHEG
90101
Promethazine (Phenergan)
Reference Values:
Reference Range: < 150 ng/mL

FIBDD
57459
PROMETHEUS IBD sgi Diagnostic
Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

FPLAC
91783
PROMETHEUS LactoTYPE
Reference Values:
A final report will be attached in MayoAccess.

PFN
80295
Propafenone, Serum
Clinical Information: Propafenone (Rythmol) is a class 1C cardiac antiarrhythmic used to treat ventricular arrhythmias (ventricular tachycardia, supraventricular tachycardia, and ventricular premature contractions). Propafenone undergoes extensive first metabolism (half-life is approximately 1-3 hours). Its clinical efficacy is maintained through the formation of a metabolite (5-hydroxypropafenone) that is more pharmacologically active than the parent drug and has a longer half-life (6-12 hours). Specimens should only be collected after patient has been receiving propafenone orally for at least 3 days. Trough concentrations should be collected just before administration of the next dose. The therapeutic concentration is 0.5-2.0 mcg/mL; concentrations less than 0.5 mcg/mL likely indicate inadequate therapy, and propafenone above 2.0 mcg/mL indicates excessive therapy. Adverse side effects are seen in the central nervous system, skin, and gastrointestinal tract.

Useful For: Monitoring propafenone therapy Assessing potential toxicity
**Interpretation:** The therapeutic concentration is 0.5 to 2.0 mcg/mL; concentrations below 0.5 mcg/mL likely indicate inadequate therapy and propafenone above 2.0 mcg/mL indicates excessive therapy.

**Reference Values:**

- Trough Value
  - 0.5-2.0 mcg/mL: Therapeutic concentration
  - >2.0 mcg/mL: Toxic concentration

**Clinical References:**


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**Propofol, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

Synonym(s): Diprivan

Patients required a mean blood propofol concentration of 4.05 +/- 1.01 mcg/mL for major surgery and 2.97 +/- 1.07 mcg/mL for non-major surgery. Blood propofol concentrations at which 50% of patients were awake and oriented after surgery were 1.07 and 0.95 mcg/mL respectively.

Psychomotor performance returned to baseline at blood propofol concentrations of 0.38 - 0.43 mcg/mL.

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**Prostaglandin D2 (PG D2), Urine**

**Clinical Information:** Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2, and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord, intestines, and stomach. Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and indomethacin.

**Reference Values:** No reference intervals available for this test.

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**Prostaglandin D2 (PGD2)**

**Clinical Information:** Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2, and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord,
Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and Indomethacin.

**Reference Values:**

Adult Reference Range(s): 35 - 115 pg/mL

No pediatric reference ranges available for this test.

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**PHI11**

**113000**

**Prostate Health Index Reflex, Serum**

**Clinical Information:** Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. In conditions of increased glandular size and tissue damage, PSA is released into circulation. Measurement of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment. PSA is also used as a screening tool for prostate cancer detection, although its use in screening has become controversial in recent years. While an elevated serum PSA is associated with prostate cancer, a number of benign conditions, such as benign prostatic hyperplasia (BPH) and prostatitis might lead to elevated serum PSA concentrations. As a consequence PSA lacks specificity for prostate cancer detection. Several PSA isoforms have been identified that can further increase the specificity of PSA for prostate cancer. In particular, the [-2] form of proPSA (p2PSA) shows improved performance over either total or free PSA for prostate cancer detection on biopsy. The prostate health index (phi) is a formula that combines all 3 PSA forms (total PSA, free PSA, and p2PSA) into a single score. phi is calculated using the following formula: (p2PSA/free PSA) x square root of PSA. In a multicenter study that compared the performance of PSA, free PSA, p2PSA, and phi in men undergoing prostate biopsy due to a serum PSA concentration between 4 and 10 ng/mL, phi was the best predictor of any prostate cancer, high-grade cancer, and clinically significant cancer. At 95% clinical sensitivity, the clinical specificity of phi was 16.0%, compared to 8.4% for free PSA and 6.5% for PSA. Prostatic biopsy is required for diagnosis of cancer.

**Useful For:** Aiding in distinguishing prostate cancer from benign prostate conditions in men with prostate-specific antigen (PSA) concentrations in the 4 to 10 ng/mL range and digital rectal examination (DRE) findings that are not suspicious for cancer Calculation of prostate health index (phi) as a part of a reflex test when PSA concentrations are between 4 and 10 ng/mL

**Interpretation:** Prostate health index (phi) may be used to determine the probability of prostate cancer on biopsy in men with total prostate-specific antigen (PSA) in the 4 to 10 ng/mL range. Low phi scores are associated with a lower probability of finding prostate cancer on biopsy and higher phi scores are associated with an increased probability of finding prostate cancer on biopsy. The choice of an appropriate phi score to be used in guiding clinical decision-making may vary for each patient and may depend on other clinical factors or on family history of disease. The table below indicates the probability of finding prostate cancer on biopsy when PSA is the in range of 4 to 10 ng/mL and may be used as guidance for interpreting the phi score. phi range Probability of cancer 95% Confidence interval 0-26.9 9.8% 5.2%-15.4% 27.0-35.9 16.8% 11.3%-22.2% 36.0-54.9 33.3% 26.8%-39.9% 55.0+ 50.1% 39.8%-61.0%

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =2.0 ng/mL.</td>
<td></td>
</tr>
<tr>
<td>40-49 years</td>
<td>&lt; or =2.5 ng/mL.</td>
</tr>
<tr>
<td>50-59 years</td>
<td>&lt; or =3.5 ng/mL.</td>
</tr>
<tr>
<td>60-69 years</td>
<td>&lt; or =4.5 ng/mL.</td>
</tr>
</tbody>
</table>
70-79 years  < or = 6.5 ng/mL.
> or = 80 years  < or = 7.2 ng/mL
PERCENT FREE PSA: When PSA is in the range of 4-10 ng/mL

<table>
<thead>
<tr>
<th>% Free PSA</th>
<th>Probability of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =</td>
<td>56%</td>
</tr>
<tr>
<td>11-15%</td>
<td>28%</td>
</tr>
<tr>
<td>16-20%</td>
<td>20%</td>
</tr>
<tr>
<td>21-25%</td>
<td>16%</td>
</tr>
<tr>
<td>&gt;25%</td>
<td>8% PROSTATE HEALTH INDEX (phi)</td>
</tr>
</tbody>
</table>

Males: When PSA is in the range of 4-10 ng/mL.

<table>
<thead>
<tr>
<th>phi range</th>
<th>Probability of cancer</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-26.9</td>
<td>9.8%</td>
<td>5.2-15.4%</td>
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<td>27.0-35.9</td>
<td>16.8%</td>
<td>11.3-22.2%</td>
</tr>
<tr>
<td>36.0-54.9</td>
<td>33.3%</td>
<td>26.8-39.9%</td>
</tr>
<tr>
<td>&gt; or = 55.0</td>
<td>50.1%</td>
<td>39.8-61.0%</td>
</tr>
</tbody>
</table>

**Clinical References:**

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**Prostate Specific Antigen (PSA) Immunostain, Technical Component Only**

**Clinical Information:** Prostate specific antigen is present within the cytoplasm of glandular epithelium in normal prostate, as well as in prostate cancer. It is useful diagnostically for identification of adenocarcinoma of the prostate in metastatic sites and for differentiating prostatic adenocarcinoma from urothelial carcinoma.

**Useful For:** Marker of glandular epithelium in normal and neoplastic prostate

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Prostate Tumor, FISH, Tissue**

**Clinical Information:** The tumor suppressor gene PTEN is often altered in patients with prostate cancer. Patients with advanced tumors have a deletion of the PTEN gene locus. Rearrangement or separation may be another mechanism responsible for inactivation of the PTEN gene. FISH analysis allows for the detection of deletion, homozygous deletion, and rearrangement of the PTEN gene region.

**Useful For:** Identifying PTEN gene deletion or rearrangements in patients with prostatic adenocarcinoma

**Interpretation:** A positive result with the PTEN probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of PTEN suggests inactivating structural alterations of the PTEN gene region at 10q23. A negative result suggests no structural alterations of the locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Prostate-Specific Antigen (PSA) Diagnostic, Serum**

**Clinical Information:** Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50, and also for those men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

**Useful For:** Evaluating patients with documented prostate problems in whom multiple prostate-specific antigen tests may be necessary per year Monitoring patients with a history of prostate cancer as an early indicator of recurrence and response to treatment

**Interpretation:** Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hypertrophy. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but further testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values above 0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.
Reference Values:

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>PSA Upper Limit (ng/mL)</th>
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<tbody>
<tr>
<td>&lt; or =2.0</td>
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<tr>
<td>70-79</td>
<td>&lt; or =6.5</td>
</tr>
<tr>
<td>&gt; or =80</td>
<td>&lt; or =7.2 Females: not applicable</td>
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Prostate-Specific Antigen (PSA) Screen, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50, and for those men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

Useful For: Monitoring patients with a history of prostate cancer as an early indicator of recurrence and response to treatment Prostate cancer screening

Interpretation: Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but additional testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values above 0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.

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50-59  < or =3.5
60-69  < or =4.5
70-79  < or =6.5
> or =80  < or =7.2 Females: not applicable


Prostate-Specific Antigen (PSA) Ultrasensitive, Serum

Clinical Information: Prostate-specific antigen (PSA) is the most widely used method to detect prostate cancer recurrence after radical prostatectomy (RP). Approximately 20% to 35% of patients develop a rising PSA following RP for clinically localized prostate cancer. Biochemical recurrence (BCR) is defined as an increase in PSA after curative therapy without clinical or radiological evidence of disease. The median time to BCR could vary between 2 to 3 years. A standard PSA cutpoint to indicate BCR has yet to be established. For example, the American Urological Association and the American Society for Radiation Oncology defined BCR after surgery as initial and confirmatory PSA concentrations of 0.2 ng/mL or greater. However, a BCR definition of 0.4 ng/mL PSA has also been proposed. Assays that measure PSA to concentrations below 0.1 ng/mL are denoted ultrasensitive PSA (USPSA). The use of USPSA cutpoints below currently recommended PSA thresholds may be helpful in identifying cases of early biochemical recurrence and for selecting patients with adverse clinicopathologic risk factors for secondary therapy. However, some authors believe that USPSA assays offers minimal advantages and could lead to increased anxiety in patients who have clinically meaningless rises of PSA and might lead to overtreatment.

Useful For: Monitoring disease after radical prostatectomy This test should not be used for initial prostate cancer screening.

Interpretation: An undetectable (<0.01 ng/mL) ultrasensitive prostate-specific antigen (USPSA) concentration after radical prostatectomy is reassuring and may aid in postoperative risk stratification of patients. A detectable USPSA concentration (> or =0.01 ng/mL) after radical prostatectomy (RP) does not necessarily translate into disease progression or recurrence. Interpretation of a detectable USPSA needs to be made in conjunction with other clinicopathologic risk factors. The cutpoint for interpretation of USPSA assays remains controversial and has ranged from 0.01 to 0.05 ng/mL. For example, in a study that included 754 men after RP, a cutpoint of 0.01 ng/mL was an independent predictor of biochemical recurrence (BCR). BCR-free survival at 5 years was 92.4% for patients with an USPSA post-RP of less than 0.01 ng/mL and 56.8% for patients with an USPSA post-RP of 0.01 ng/mL or higher.(1) In the same study a cutoff of 0.03 ng/mL also predicted BCR independent of clinicopathologic factors and BCR-free survival at 5 yrs was 90.8% for patients with an USPSA post-RP of less than 0.03 ng/mL and 26.9% for patients with a PSA post-RP of greater or equal to 0.03 ng/mL.(1)

Reference Values:

Age (years)  PSA upper limit (ng/mL)
PSAFT 81944

Prostate-Specific Antigen (PSA), Total and Free, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. PSA exists in serum in multiple forms: complexed to alpha-1-anti-chymotrypsin (PSA-ACT complex), unbound (free PSA), and enveloped by alpha-2-macroglobulin (not detected by immunoassays). Higher total PSA levels and lower percentages of free PSA are associated with higher risks of prostate cancer. Most prostate cancers are slow growing, so the utility of prostate cancer screening is marginal in most men with a life expectancy of less than 10 years.

Useful For: Assessing the risk of prostate cancer in patients with borderline or moderately increased total PSA (4.0-10.0 ng/mL) Determining which patients should have follow-up prostate biopsy

Interpretation: When total prostate-specific antigen (PSA) concentration is below 2.0 ng/mL, the probability of prostate cancer in asymptomatic men is low, further testing and free PSA may provide little additional information. When total PSA concentration is above 10.0 ng/mL, the probability of cancer is high and prostate biopsy is generally recommended. The total PSA range of 4.0 to 10.0 ng/mL has been described as a diagnostic "gray zone," in which the free:total PSA ratio helps to determine the relative risk of prostate cancer (see table below). Therefore, some urologists recommend using the free:total ratio to help select which men should undergo biopsy. However, even a negative result of prostate biopsy does not rule-out prostate cancer. Up to 20% of men with negative biopsy results have subsequently been found to have cancer. Based on free:total PSA ratio: the percent probability of finding prostate cancer on a needle biopsy by age in years: Free:total PSA ratio 50-59 years 60-69 years 70 years and older < or =0.10 49% 65% 65% 0.11-0.18 27% 34% 41% 0.19-0.25 18% 24% 30% >0.25 9% 12% 16%

**Prostatic Acid Phosphatase (PACP) Immunostain, Technical Component Only**

**Clinical Information:** Prostatic acid phosphatase (PACP) is a cytoplasmic enzyme produced in normal prostatic epithelium and prostatic adenocarcinoma. PACP is a useful adjunct to the immunostain for prostate-specific antigen; if 1 of these 2 markers is immunoreactive, a tumor of prostatic origin is likely. Bladder epithelium and certain neuroendocrine tumors such as rectal carcinoid may be weakly immunoreactive.

**Useful For:** Enzyme produced in normal prostatic epithelium and prostatic adenocarcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Prostatic Acid Phosphatase, Serum**

**Clinical Information:** Prostatic acid phosphatase (PAP), a glycoprotein synthesized by the prostate gland, is a member of a diverse group of isoenzymes that are capable of hydrolyzing phosphate esters in acidic medium. They are classified on the basis of their electrophoretic mobilities. PAP was a major tumor marker for prostate cancer for more than 50 years. However, PAP is no longer used to screen for or stage prostate cancer. In most instances, serum prostate specific antigen (PSA) is used instead. PAP usefulness is now limited to niche applications. Pre-treatment PAP measurement may add unique, clinically useful prognostic information for predicting recurrence in men who are undergoing radical prostatectomy. PAP also may be useful for following the progression of disease response to therapy in men treated by androgen ablation. However, for both of these applications, PSA provides more information and also should be utilized.

**Useful For:** Aiding in predicting recurrence after radical prostatectomy for clinically localized prostate cancer Following response to androgen ablation therapy, when used in conjunction with prostate-specific antigen

**Interpretation:** Prostatic acid phosphatase (PAP) levels above the reference range may indicate prostate cancer, but can be due to many other factors, see Cautions. A rise in PAP levels in patients with known prostate cancer can indicate tumor progression or recurrence. However, there is considerable intra-subject biological variability, limiting the usefulness of this test.

**Reference Values:**
< or =2.1 ng/mL

**Clinical References:**
**Protein C Activity, Plasma**

**Clinical Information:** Physiology: Protein C is a vitamin K-dependent anticoagulant proenzyme. It is synthesized in the liver and circulates in the plasma. The biological half-life of plasma protein C is approximately 6 to 10 hours, similar to the relatively short half-life of coagulation factor VII. Protein C is activated by thrombin, in the presence of an endothelial cell cofactor (thrombomodulin), to form the active enzyme activated protein C (APC). APC functions as an anticoagulant by proteolytically inactivating the activated forms of coagulation factors V and VIII (factors Va and VIIIa). APC also enhances fibrinolysis by inactivating plasminogen activator inhibitor (PAI-1). Expression of the anticoagulant activity of APC is enhanced by a cofactor, protein S, another vitamin K-dependent plasma protein. Pathophysiology: Congenital homozygous protein C deficiency results in a severe thrombotic diathesis, evident in the neonatal period and resembling purpura fulminans. Congenital heterozygous protein C deficiency may predispose to thrombotic events, primarily venous thromboembolism; arterial thrombosis (stroke, myocardial infarction, etc.) may occur. Some individuals with hereditary heterozygous protein C deficiency may have no personal or family history of thrombosis and may or may not be at increased risk. Congenital heterozygous protein C may predispose to development of coumarin-associated skin necrosis. Skin necrosis has occurred during the initiation of oral anticoagulant therapy. Two types of hereditary heterozygous protein C deficiency are recognized: - Type I (concordantly decreased protein C function and antigen) - Type II (decreased protein C function with normal antigen level) Acquired deficiencies of protein C may occur in association with: - Vitamin K deficiency - Oral anticoagulation with coumarin compounds - Liver disease - Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) The clinical hemostatic significance of acquired protein C deficiency is uncertain. Assay of protein C functional activity is recommended for the initial laboratory evaluation of patients suspected of having congenital protein C deficiency (personal or family history of thrombotic diathesis), rather than assay of protein C antigen (PCAG / Protein C Antigen, Plasma).

**Useful For:** As an initial test for evaluating patients suspected of having congenital protein C deficiency, including those with personal or family histories of thrombotic events Detecting and confirming congenital type I and type II protein C deficiencies Detecting and confirming congenital homozygous protein C deficiency Identifying decreased functional protein C of acquired origin (eg, due to oral anticoagulant effect, vitamin K deficiency, liver disease, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

**Interpretation:** Values below 60% to 70% may represent a congenital deficiency state, if acquired deficiencies can be excluded. Protein C activity (and antigen) is generally undetectable in individuals with severe, homozygous protein C deficiency. Oral anticoagulant therapy (warfarin, Coumadin) decreases protein C activity, compromising the ability to distinguish between congenital and acquired protein C deficiency. Concomitant measurement of the activity of coagulation factor VII (or factor X) may aid in differentiating congenital deficiency state from acquired protein C deficiency due to oral anticoagulant effect, but the ratio of the activities of protein C:factor VII (or factor X) has not been demonstrated to provide certainty about this distinction. The clinical significance of acquired protein C deficiency and of increased protein C is unknown.

**Reference Values:**

70-150%

Protein C Deficiency, PROC Gene, Next-Generation Sequencing, Varies

Clinical Information: Protein C is a vitamin K-dependent plasma glycoprotein synthesized in the liver. After secretion, protein C circulates in blood mostly in its inactive form until cleaved at residues Arg211-Leu212 to form activated protein C. Activated protein C and its cofactor, protein S, act as a potent anticoagulant by cleaving and inactivating procoagulant factors VIIIa and Va. A deficiency of protein C results in impairment of the ability to control coagulation through the inactivation of procoagulant factors, factor Va and factor VIIIa, leading to an increased risk of venous thrombosis. While protein C deficient individuals are 7 to 10 times more likely to develop venous thromboembolism (VTE), 3% to 9% of these individuals actually develop a VTE, and the annual risk of VTE is between 0.4% and 1.0% per year. (1) Congenital protein C deficiency is classified into two types. Type I deficiency is characterized by decreased protein synthesis or increased intracellular protein degradation that lead to lower levels of protein C in blood. Type I deficiency accounts for about 75% of all cases of congenital protein C deficiency. Type II deficiency is characterized by dysfunctional protein C that is produced in normal amounts. There appears to be no clinical differences between type I and type II phenotypes. Protein C antigen testing (PCAG / Protein C Antigen, Plasma) is helpful to distinguish between type I and type II deficiencies and in cases where genetic testing results yield variants of uncertain significance (VUS). The PROC gene encodes for protein C. Pathogenic alterations in the gene can cause congenital protein C deficiency. Congenital protein C deficiency is inherited as an autosomal dominant disorder but with variable penetrance. Both men and women can be affected. The estimated prevalence of protein C deficiency ranges from 200 to 400 per 100,000. Individuals who are heterozygous for a pathogenic PROC alteration are at increased risk for VTE and warfarin-induced skin necrosis. The co-inheritance of additional thrombotic risk factors, eg, factor V Leiden, can compound this risk, leading to a clinically significant disorder. Homozygosity or compound heterozygosity for pathogenic alterations in the PROC gene is associated with severe protein C deficiency, which presents in infancy as the development of cerebral vein thrombosis or neonatal purpura fulminans (ie, widespread cutaneous hemorrhage and tissue death due to thrombosis of the microvascular.) These infants typically have protein C levels that virtually undetectable. Severe protein C deficient patients with very low but detectable protein C levels typically present with thromboembolic disease during early childhood or adulthood. (2) Causes of acquired (non-genetic) protein C deficiency that should be excluded prior to genetic testing include vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, and intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC).

Useful For: Ascertaining a pathogenic alteration in the PROC gene of patients with congenital protein C deficiency This test is not intended for prenatal diagnosis

Interpretation: An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, and Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.
Reference Values:
An interpretive report will be provided.


FPCTA 75735

Protein C, Total Antigen

Interpretation: Patients on warfarin may have decreased protein C values. Patients should be off warfarin therapy for two weeks for accurate measurement of protein C.

Reference Values:
- 1-4 days: 17-53%
- 5-29 days: 20-64%
- 30-89 days: 21-65%
- 90-179 days: 28-80%
- 180-364 days: 37-81%
- 1-5 years: 40-92%
- 6-10 years: 45-93%

PCTRL 607249

Protein Catabolic Rate, 24 Hour, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (e.g., citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (e.g., calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

Useful For: Calculation to measure the protein catabolic rate  Estimation of dietary protein intake

Interpretation: Increased protein intake, reflected by an increased protein catabolic rate, may increase the risk of kidney stone formations.

Reference Values:
Only orderable as part of a profile. For more information see SAT24 / Supersaturation Profile, 24 Hour, Urine.

- 56-125 g/24 hours

**Protein Electrophoresis and Isotype, Serum**

**Clinical Information:** This profile includes total protein, protein electrophoresis, and M-protein isotyping. The serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and complement C3 -Gamma, composed primarily of immunoglobulins (Ig) The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases. The following algorithms are available in Special Instructions: -Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Diagnosis of monoclonal gammopathies, when used in conjunction with locally performed serum free light chain studies (performed at client site)

**Interpretation:** Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Immunoaffinity purification followed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL respectively, should be followed by VISCS / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and SPE should not be used to screen for the disorder. DMOGA / Monoclonal Gammopathy, Diagnostic, Serum which includes MALDI-TOF MS and serum free light chains, should be done to screen if the clinical suspicion is high. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergamaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).
Reference Values:

TOTAL PROTEIN

> or =1 year: 6.3-7.9 g/dL

Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS

Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report.

Reference values have not been established for patients that are <16 years of age.

M-PROTEIN ISOTYPE MALDI-TOF MS, S

No monoclonal protein detected

M-protein Isotype MALDI-TOF MS Flag
Negative


Protein S Activity, Plasma

Clinical Information: Protein S is a vitamin K-dependent plasma glycoprotein synthesized predominantly within the liver. Protein S is also synthesized in endothelial cells and present in platelets. As a part of the plasma anticoagulant system, protein S acts as a necessary cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. About 60% of the total plasma protein S antigen circulates bound to C4b binding protein (C4b-BP), while the remainder circulates as "free" protein S. Only free protein S has anticoagulant activity. Congenital protein S deficiency is an autosomal codominant disorder that is present in 1% to 3% of patients with venous thromboembolism. Heterozygous protein S deficiency carriers have approximately a 10-fold increased risk of venous thromboembolism. Other phenotypic expressions of heterozygous congenital protein S deficiency include recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placenta, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of heterozygous congenital protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S (APC cofactor) activity in plasma. Types of Heterozygous Protein S Deficiency Type Protein S Antigen, Free Protein S Antigen, Total Protein Activity I Decreased Decreased Decreased II Normal Normal Decreased III Decreased Normal Decreased Type I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4b-BP. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) caused by the absence or near absence of plasma protein S. Acquired deficiency of protein S is much more common than hereditary protein S deficiency and is generally of unknown hemostatic significance (ie, uncertain thrombosis risk). Among the many causes of acquired protein S deficiency are: -Vitamin K deficiency -Oral anticoagulant therapy -Acute illness (eg, acute thrombosis, recent surgery, or other disorder associated with acute inflammation) -Liver disease -ICF/DIC -Thrombotic thrombocytopenic purpura -Pregnancy, oral contraceptive, or estrogen therapy -Nephrotic syndrome -Sickle cell anemia

Useful For: Second-order testing for diagnosis of congenital or acquired protein S deficiency for example, as an adjunct to initial testing based on results of protein S antigen assay (free protein S antigen, with or without total protein S antigen assay) Evaluating patients with a history of venous
Interpretation: In type I and type III congenital deficiency, free protein S antigen is decreased and protein S functional activity is similarly decreased. In type II congenital (dysfunctional) protein S deficiency, total and free protein S antigen levels are normal but functional activity is decreased. Patients with acquired free protein S deficiency associated with inflammation-related increase of C4b-binding protein (C4b-BP) typically have decreased free protein S antigen (and protein S activity) and normal (or elevated) total protein S antigen. Acquired protein S deficiency is of uncertain clinical hemostatic significance and is associated with a variety of conditions. Elevated protein S levels are of uncertain clinical significance.

Reference Values:
Males: 65-160%
Females
<50 years: 50-160%
≥50 years: 65-160%
Newborn infants have normal or near-normal free protein S antigen (> or =50%), although total protein S antigen is usually below the adult reference range. There are insufficient data concerning protein S activity in normal neonates, infants, and children; but normal or near-normal activity (> or =50%) probably is present by age 3 to 6 months.


Protein S Antigen, Free, Plasma

Clinical Information: Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the complement regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP while the remaining 40% circulates as "free" protein S. Only free protein S has anticoagulant function, C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placenta, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4bBP-beta.
Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown haemostatic significance (ie, uncertain thrombosis risk), and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy or estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

**Useful For:** As part of an investigation of patients with a history of thrombosis. See profile PSTF / Protein S Antigen, Plasma.

**Interpretation:** Protein S values vary widely in the normal population and are age- and sex-dependent. Types of Heterozygous Protein S Deficiency Type Protein S Deficiency Type Protein S Antigen Free Protein S Antigen Total Protein S Activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4bBP are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, S_FX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful, but is generally not yet available.

**Reference Values:**
Only orderable as part of a profile, see PSTF / Protein S Antigen, Plasma.

Males: 65-160%
Females:
<50 years: 50-160%
> or =50 years: 65-160%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15%-50%), but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (> or =50%). Total protein S reaches adult levels by 90-180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing in Special Instructions.

Protein S Antigen, Plasma

Clinical Information: Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the complement regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP while the remaining 40% circulates as "free" protein S. Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition, they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placenta, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to variants within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown hemostatic significance (ie, uncertain thrombosis risk) and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy, estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

Useful For: Investigation of patients with a history of thrombosis

Interpretation: Protein S values vary widely in the normal population and are age- and sex-dependent. Types of Heterozygous Protein S Deficiency Type Protein S antigen free Protein S antigen total Protein S activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4b-binding protein (C4bBP) are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, S_FX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free
Protein S antigen suggests vitamin K deficiency or a warfarin (Coumadin) effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful; see PRSNG / Protein S Deficiency, PROS1 Gene, Next-Generation Sequencing, Varies.

Reference Values:
TOTAL
- Males: 80-160%
- Females
  - <50 years: 70-160%
  - ≥50 years: 80-160%

FREE
- Males: 65-160%
- Females
  - <50 years: 50-160%
  - ≥50 years: 65-160%

Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15-50%); but because of low levels of C4b-binding protein, free protein S may be normal or near the normal adult level (≥50%). Total protein S reaches adult levels by 90 to 180 days postnatal.

Clinical References:

Protein S Antigen, Total, Plasma

Clinical Information: Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the compliment regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP, while the remaining 40% circulates as free protein S.
Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown hemostatic significance (ie, uncertain thrombosis risk), and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy or estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

**Useful For:** Investigation of patients with a history of thrombosis

**Interpretation:** Protein S values vary widely in the normal population and are age- and sex-dependent. Types of Heterozygous Protein S Deficiency Type Protein S Antigen Free Protein S Antigen Total Protein S Activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4bBP are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, S_FX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, the presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful, but is generally not yet available.

**Reference Values:**

Only orderable as part of a profile. For more information see PSTF / Protein S Antigen, Plasma.

Males: 80-160%
Females:
<50 years: 70-160%
> or ≥50 years: 80-160%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15%-50%), but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (> or ≥50%). Total protein S reaches adult levels by 90-180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and

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**Protein S Deficiency, PROS1 Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Protein S (PS) is a vitamin K-dependent glycoprotein that is synthesized mainly in the liver and endothelium and is part of the natural anticoagulant system. It is a cofactor in the inactivation of procoagulant factors V and VIII. Most (60%) of protein S circulates in plasma in a form bound to C4b binding protein and the rest circulates freely and is termed "free PS". The free form serves as a cofactor to anticoagulant enzyme activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. A congenital deficiency of protein S deficiency increases thrombotic risk by 8-10 fold compared to normal individuals. Nearly half of PS type I deficiency patients present with venous thromboembolism (VTE) until the age of 55; about half of these VTE events are unprovoked (1). The use of oral contraceptives in women deficient in protein S may increase the risk of VTE by 600-fold compared to individuals with normal PS levels. Women with PS deficiency also have a 3-fold increased risk for pregnancy loss and pregnancy complications (1). The prevalence of congenital protein S deficiency in the general population is 0.16% to 0.21%. The prevalence of protein S deficiency in patients with VTE is estimated to be 2% (2). Congenital protein S deficiency is classified into three disease states. In type I PS deficiency, there is a decreased amount of both bound and free forms of protein S. In type II deficiency, protein function is altered but levels of protein S are normal. In type III deficiency, there is a low level of free protein S but a normal amount of total protein S. No differences in clinical presentation and severity have been observed for the different phenotypes. The PROS1 gene encodes for protein S (PS). Alterations in PROS1 can lead to sustained activation of factors V and VIII and the continued production of thrombin, leading to an increased risk for thrombosis. Congenital protein S deficiency is inherited in an autosomal dominant manner with incomplete penetrance. Heterozygotes for a pathogenic alteration in PROS1 typically present with plasma protein S levels in the 35% to 60% range (3). Individuals who are homozygous or compound heterozygous for pathogenic alterations in PROS1 present with massive VTE or neonatal purpura fulminans, which is life-threatening if untreated. Retinopathy has also been observed as the presenting symptoms in some cases. Genetic testing of the PROS1 gene is indicated if free protein S antigen or activity is abnormally reduced and acquired causes of protein S deficiency have been excluded. Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15%-50%); but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (greater than or equal to 50%). Total protein S reaches adult levels by 90 to 180 days postnatal. Acquired (non-genetic causes) of protein S deficiency are much more common than hereditary protein S deficiency. It is unknown if acquired deficiency of protein S results in increased thrombotic risk. Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC), thrombotic thrombocytopenia purpura (TTP), pregnancy or estrogen therapy, and nephritic syndrome are common acquired causes of protein S deficiency. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Additionally, many preanalytic factors may interfere with measurements of free and total protein S, such as the use of heparin, having hemoglobin levels greater than 20 g/dL, bilirubin (greater than 25 mg/dL for free protein S, greater than 100 mg/L for total protein S), or rheumatoid factor greater than 900 IU/mL. Free protein S measurements are affected by additional factors such as elevated triglycerides (greater than 1,500 mg/dL), sickle cell anemia, and the presence of the factor V Leiden alteration in the F5 gene.

**Useful For:** Ascertaining a pathogenic alteration in the PROS1 gene of patient with congenital
**Protein, Total, 12 Hour, Urine**

**Clinical Information:** Protein in urine normally consists of plasma proteins that have been filtered by glomeruli and not reabsorbed by the proximal tubule, and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: increased plasma concentration of proteins that exceeds capacity for proximal tubular reabsorption (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor -Preeclampsia -Orthostatic proteinuria In pregnant women, a urinary protein excretion of more than 300 mg/24 hours is frequently cited as consistent with preeclampsia and 12-hour total protein excretion highly correlates with 24-hour values in this patient population. (1,2) Orthostatic proteinuria is characterized by increased protein excretion in the upright position but normal levels when supine. This condition can be detected by comparing urine protein levels in a collection split between day and night (see OPTU / Orthostatic Protein, Timed Collection, Urine). Orthostatic proteinuria is common in childhood and adolescence but rare after 30 years of age.

**Useful For:** Evaluation of renal disease Screening for monoclonal gamopathy Screening for postural (orthostatic) proteinuria In select clinical situations, collection of a 12-hour specimen may allow more rapid detection of proteinuria states (eg, screening pregnant patients for preeclampsia)

**Interpretation:** Total urine protein determined to be greater than 500 mg/24 hours should be evaluated by immunofixation to assess if there is a monoclonal immunoglobulin light chain and, if present, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

**Reference Values:**

<163 mg/12 hours (day or night collection)

Reference values have not been established for patients <18 years of age.


Protein, Total, 24 Hour, Urine

**Clinical Information:** Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor

**Useful For:** Evaluation of kidney disease using a 24-hour urine collection Screening for monoclonal gammopathy

**Interpretation:** Total protein greater than 500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present, and if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

**Reference Values:**

> or =18 years: <229 mg/24 hours

Reference values have not been established for patients <18 years of age.

Reference value applies to 24-hour collection.

**Clinical References:**


Protein, Total, Body Fluid

**Clinical Information:** Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end stage renal disease, and heart failure that can lead to excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Dr. Richard Light derived criteria in the 1970s that are still used today for patients with pleural effusions.(2) The criteria include the measurement of total protein and lactate dehydrogenase (LDH) in pleural fluid and serum. Exudates are defined as meeting 1 of the
following criteria: 1. Pleural fluid to serum protein ratio above 0.5 2. Pleural fluid LDH above two-thirds the upper limit of normal serum LDH 3. Pleural fluid to serum LDH ratio above 0.6 Dr. Light's criteria were designed to be sensitive for detecting exudates at the expense of specificity.(3) Heart failure and recent diuretic use contribute to most misclassifications by Dr. Light's criteria (transudates falsely categorized as exudates). Serum-to-fluid protein gradient (serum protein minus fluid protein) may be calculated in these cases and when more than 3.1 g/dL suggests the patient has a transudative effusion. Peritoneal fluid: The pathologic accumulation of fluid within the peritoneal cavity is commonly referred to as ascites. The most common cause of ascites is liver cirrhosis. Differentiating cardiac from cirrhotic ascites is a common clinical conundrum as they are common conditions presenting with elevated serum ascites albumin gradient (SAAG).(4) Heart failure leads to the development of high gradient ascites due to hepatic sinusoidal hypertension. Since the sinusoids are normal and have not been damaged from collagen deposition associated with cirrhosis, protein tends to "leak" more readily into ascites and is associated with higher total protein concentrations.

**Useful For:** Identification of exudative pleural effusions Differentiating hepatic from other causes of ascites that have elevated serum ascites albumin gradient (SAAG) using peritoneal fluid

**Interpretation:** A pleural fluid total protein to serum total protein ratio of above 0.5 is most consistent with exudative effusion.(2,5) A peritoneal fluid total protein of above 2.5 g/dL in patients with a high serum ascites albumin gradient (SAAG) can be caused by heart failure. A peritoneal fluid total protein of over 1.0 g/dL helps to differentiate secondary from spontaneous bacterial peritonitis in conjunction with other laboratory, imaging and clinical findings.(6,7,8) The usefulness of measuring total protein in pericardial fluid is not well documented. Results may be interpreted in conjunction with serum or plasma total protein concentrations. The usefulness of measuring total protein in synovial fluid is limited as it has poor sensitivity and specificity for differentiating inflammatory vs non-inflammatory causes and should be interpreted in conjunction with other clinical findings.(9) All other fluids: Total protein may be used to differentiate transudative from exudative effusions. The decision limits are not well defined in fluids other than pleural fluid and should be interpreted in conjunction with other clinical findings.(10)

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Protein, Total, Serum**

**Clinical Information:** Plasma proteins are synthesized predominantly in the liver; immunoglobulins are synthesized by mononuclear cells of lymph nodes, spleen and bone marrow. The 2 general causes of alterations of serum total protein are a change in the volume of plasma water and a change in the concentration of 1 or more of the specific proteins in the plasma. Of the individual serum proteins, albumin is present in such high concentrations that low levels of this protein alone may cause hypoproteinemia. Hemoconcentration (decrease in the volume of plasma water) results in relative hyperproteinemia; hemodilution results in relative hypoproteinemia. In both situations, concentrations of all the individual plasma proteins are affected to the same degree. Hyperproteinemia may be seen in

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**TP**

8520

**Protein, Total, Serum**

**Clinical Information:** Plasma proteins are synthesized predominantly in the liver; immunoglobulins are synthesized by mononuclear cells of lymph nodes, spleen and bone marrow. The 2 general causes of alterations of serum total protein are a change in the volume of plasma water and a change in the concentration of 1 or more of the specific proteins in the plasma. Of the individual serum proteins, albumin is present in such high concentrations that low levels of this protein alone may cause hypoproteinemia. Hemoconcentration (decrease in the volume of plasma water) results in relative hyperproteinemia; hemodilution results in relative hypoproteinemia. In both situations, concentrations of all the individual plasma proteins are affected to the same degree. Hyperproteinemia may be seen in
dehydration due to inadequate water intake or to excessive water loss (eg, severe vomiting, diarrhea, Addison disease, and diabetic acidosis) or as a result of increased production of proteins. Increased polyclonal protein production is seen in reactive, inflammatory processes; increased monoclonal protein production is seen in some hematopoietic neoplasms (eg, multiple myeloma, Waldenstrom macroglobulinemia, monoclonal gammopathy of undetermined significance).

**Useful For:** Diagnosis and treatment of a variety of diseases involving the liver, kidney, or bone marrow, as well as other metabolic or nutritional disorders

**Interpretation:** Mild hyperproteinemia may be caused by an increase in the concentration of specific proteins normally present in relatively low concentration, eg, increases in acute phase reactants and polyclonal immunoglobulins produced in inflammatory states, late-stage liver disease, and infections. Moderate-to-marked hyperproteinemia may also be due to multiple myeloma and other malignant paraproteinemias, although normal total protein levels do not rule out these disorders. A serum protein electrophoresis should be performed to evaluate the cause of the elevated serum total protein. Hypoproteinemia may be due to decreased production (eg, hypogammaglobulinemia) or increased protein loss (eg, nephrotic syndrome, protein-losing enteropathy). A serum protein electrophoresis should be performed to evaluate the cause of the decreased serum total protein. If a nephrotic pattern is identified, urine protein electrophoresis should also be performed.

**Reference Values:**
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**
1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier, 2018

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**TPSF**

**Protein, Total, Spinal Fluid**

**Clinical Information:** Cerebrospinal fluid (CSF) proteins are those that remain in CSF following the ultrafiltration of plasma through the choroidal capillary wall. Some proteins that are unique to CSF are synthesized in the central nervous system. In general, diseases that interrupt the integrity of the capillary endothelial barrier lead to an increase in the total CSF protein. CSF protein is generally increased in all types of meningitis, cerebral infarction, brain abscess, meningovascular syphilis, subarachnoid hemorrhage, some brain tumors, trauma to the brain, some cases of multiple sclerosis, encephalomyelitis, and degenerative neurologic diseases. A decreased CSF protein may occur in water intoxication, CSF leak (CSF rhinorrhea or otorrhea), and hyperthyroidism.

**Useful For:** Detecting disruptions of the blood-brain barrier or intrathecal synthesis of immunoglobulins

**Interpretation:** Striking elevations of cerebrospinal fluid (CSF) total protein are noted in bacterial meningitis; smaller elevations occur in the other inflammatory diseases and with tumor or hemorrhage. The effect of any of these conditions is that the proportions of specific proteins in CSF increasingly resemble serum. In order to assess increased permeability or increased intrathecal production of proteins, simultaneous serum specimen and CSF specimens should be taken.

**Reference Values:**
> or =12 months: 0-35 mg/dL
Reference values have not been established for patients that are <12 months of age.

**Clinical References:**
Protein/Creatinine Ratio, Random, Urine

Clinical Information: Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinuria)

Useful For: Evaluation of renal disease Screening for monoclonal gammopathy

Interpretation: Total protein of greater than 500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present and, if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract. In a random urine specimen, a protein:creatinine or protein:osmolality ratio can be used to roughly approximate 24-hour excretion rates. The normal protein-to-osmolality ratio is less than 0.42. For patients younger than 18 years of age no reference range has been established.

Reference Values:
> or =18 years: <0.18 mg/mg creatinine
Reference values have not been established for patients <18 years of age.


Proteinase 3 Antibodies, IgG, Serum

Clinical Information: Proteinase 3 (PR3) antigen is a 29-kD serine protease that exists as a protein triplet in human neutrophils. Wegener granulomatosis (WG) is an autoimmune vasculitis that affects the kidneys and lungs, as well as other organs. Patients with WG develop autoantibodies to the PR3 antigen of myeloid lysosomes (PR3 antineutrophil cytoplasmic antibodies [PR3 ANCA]). Since it is often impossible to distinguish between WG and other forms of vasculitis on the basis of clinical signs and symptoms, tests for PR3 ANCA should be employed with other serologic tests in the initial diagnostic evaluation of patients with clinical features of vasculitis (eg, VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum).

Useful For: Evaluating patients suspected of having Wegener granulomatosis (WG) Distinguishing between WG and other forms of vasculitis, in conjunction with: -MPO / Myeloperoxidase Antibodies, IgG, Serum -ANCA / Cytoplasmic Neutrophil Antibodies, Serum (may be obtained as VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum) May be useful to follow treatment response or to monitor disease activity in patients with myeloperoxidase antibodies

Interpretation: Proteinase 3 antineutrophil cytoplasmic antibodies (PR3 ANCA) are detectable in
nearly all patients with severe active Wegener granulomatosis (WG). The presence of PR3 ANCA is a specific diagnostic indicator of WG; less than 2% of positive results occur in patients who do not have the disease. A negative result for PR3 ANCA diminishes the likelihood that a patient has active WG; but, approximately 20% of patients with limited WG may test negative for PR3 ANCA. The levels of PR3 ANCA often decline following successful treatment of patients with WG. Nevertheless, follow-up testing for PR3 ANCA to evaluate clinical status in treated patients should be used with caution as the levels of antibodies may correlate poorly with clinical status in some patients.

Reference Values:
- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- > or =1.0 U (positive)
Reference values apply to all ages.

Clinical References:
used for monitoring "stable" oral anticoagulation. A mixing test of patient and normal plasma (1:2) can be performed, if indicated, to differentiate coagulation factor deficiency from inhibition.

**Useful For:** Screening to identify a deficiency of one or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, X) due to hereditary deficiency or acquired conditions such as liver disease, vitamin K deficiency, or a specific factor inhibitor Monitoring patients on oral anticoagulant therapy to maintain a patient in a safe therapeutic range

**Interpretation:** Prolongation of the prothrombin time (PT) can occur as a result of deficiency of one or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. PT mixing study, using equal volume patient and normal pool plasma, may be performed on specimens with a prolonged PT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors. Correction of the PT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged PT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the PT mix typically fails to correct a prolonged PT. However, the presence of a weak inhibitor may be missed by the PT mixing study. Accurate interpretation of both PT and PT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the activated partial thromboplastin (APTT) and dilute Russell viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, APROL / Prolonged Clot Time Profile).

**Reference Values:**
Only orderable as part of a profile or reflex. For more information see:
- ALUPP / Lupus Anticoagulant Profile, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- AATHR / Thrombophilia Profile, Plasma
- APROL / Prolonged Clot Time Profile, Plasma
- ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

**Prothrombin Time**
9.4-12.5 seconds

**International Normalized Ratio (INR)**
0.9-1.1 Å
- Standard intensity warfarin therapeutic range: 2.0-3.0
- High intensity warfarin therapeutic range: 2.5-3.5

**Clinical References:** Kamal AH; Tefferi A; Pruthi RK: How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc 2007 July;82(7):864-873
more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. PT mixing study, using equal volume patient and normal pool plasma, may be performed on specimens with a prolonged PT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors. Correction of the PT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged PT is due to an inhibitor (specific coagulation factor inhibitor, lupus anticoagulant, heparin, etc), the PT mix typically fails to correct a prolonged PT. However, the presence of a weak inhibitor may be missed by the PT mixing study. Accurate interpretation of both PT and PT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the activated partial thromboplastin (APTT) and dilute Russell viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory: ALUPP / Lupus Anticoagulant Profile, Plasma ALBLD / Bleeding Diathesis Profile, Limited, Plasma AATHR / Thrombophilia Profile, Plasma APROL / Prolonged Clot Time Profile, Plasma ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

Reference Values:
Only orderable as a reflex. For more information see:
   ALUPP / Lupus Anticoagulant Profile, Plasma
   ALBLD / Bleeding Diathesis Profile, Limited, Plasma
   AATHR / Thrombophilia Profile, Plasma
   APROL / Prolonged Clot Time Profile, Plasma
   ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

   9.4-12.5 seconds


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Prothrombin Time, Plasma

Clinical Information: Prothrombin is a plasma protein with a molecular weight of 68,700 Da. It is an unstable protein that can split easily into smaller compounds, one of which is thrombin. Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so the prothrombin concentration in the plasma falls to levels too low to provide normal blood coagulation. Vitamin K is required by the liver for normal activation of prothrombin as well as other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin concentration so low that a bleeding tendency results. Prothrombin time (PT) is used as a screening test to detect a deficiency of one or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, or X) due to a hereditary or acquired deficiency, liver disease, vitamin K deficiency, or presence of inhibitors. Inhibitors include specific coagulation factor inhibitors, Lupus-like anticoagulant inhibitors (eg, antiphospholipid antibodies), and nonspecific prothrombin time inhibitors (eg, monoclonal immunoglobulins, elevated fibrin degradation products). Mixing studies with normal plasma are useful in initial evaluation of prolonged PT when the cause is unknown (eg, not attributable to known oral anticoagulation or known coagulation factor deficiency). One of the following tests may be appropriate, depending on the clinical picture: -LUPPR / Lupus Anticoagulant Profile, Plasma
   -THRMP / Thrombophilia Profile, Blood and Plasma
   -BDIAL / Bleeding Diathesis Profile, Limited, Plasma
   -PROC / Prolonged Clot Time Profile, Plasma PT results produced by different assays may vary significantly as there are differences in activity of the tissue factor and the instrument used to perform the test. Tissue factor is isolated from a variety of sources by assay manufacturers, and different
batches may have different activity. Calculation of the international normalized ratio (INR) addresses this problem by normalizing the PT result. For this reason, INR is used to monitor oral anticoagulant therapy (warfarin or Coumadin). Warfarin inhibits the enzyme vitamin K epoxide reductase complex 1 (VKORC1), which is responsible for converting vitamin K to its active, reduced form. By inhibiting VKORC1, warfarin decreases the available active form of vitamin K in the tissues. Thus, when warfarin is given to a patient, the amounts of active prothrombin and factors VII, IX, and X, all formed by the liver degrade and are replaced by inactive factors. Although the coagulation factors continue to be produced, they have greatly decreased coagulant activity. Bleeding is the primary adverse reaction associated with warfarin use, and is among the top 10 drugs with the largest number of serious adverse events reported to the FDA. For these reasons, monitoring therapy closely and adjusting dose accordingly is critical. The international sensitivity index (ISI) is an experimentally derived measurement, usually provided by the thromboplastin manufacturer, reflecting thromboplastin (and PT) sensitivity to coagulation deficiencies. More sensitive thromboplastins have a low ISI (1.0-1.2), whereas less sensitive thromboplastins have a higher ISI (eg, 2.0-3.0). Calculation of the INR is as follows: INR=(Patient's PT/mean PT of reference range) ISI where: -INR=international normalized ratio -ISI=international sensitivity index

**Useful For:** Screening assay to detect deficiencies of one or more coagulation factors (factors I, II, V, VII, X) Screening assay to detect coagulation inhibition Monitoring intensity of oral anticoagulant therapy when combined with INR reporting

**Interpretation:** Prothrombin time (PT) may be prolonged due to deficiencies of factors X, VII, V, and II of the extrinsic pathway, presence of inhibitors, or oral anticoagulation therapy. INR therapeutic ranges for orally administered drugs: -Standard-intensity warfarin therapeutic range: 2.0 to 3.0 -High-intensity warfarin therapeutic range: 2.5 to 3.5 Note: The INR should only be used for patients on stable oral anticoagulant therapy, though it is reported for all patients despite whether they are receiving oral anticoagulants.

**Reference Values:**
PROTHROMBIN TIME
9.4-12.5 seconds

INTERNATIONAL NORMALIZED RATIO (INR)
0.9-1.1

Standard intensity warfarin therapeutic range: 2.0-3.0
High intensity warfarin therapeutic range: 2.5-3.5

**Clinical References:**

**PPFWE**

**Protoporphyrins, Fractionation, Washed Erythrocytes**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDP). Clinical presentation of EPP and XLDP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by diminished ferrochelatase resulting in significantly increased free protoporphyrin levels.
in erythrocytes, plasma, and feces. XLDPP is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin in plasma and feces. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PPFE / Protoporphyrins, Fractionation, Whole Blood -PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Preferred test for analysis of erythrocyte protoporphyrin fractions Preferred test for evaluating patients with possible diagnoses of erythropoietic protoporphyria and X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria, or X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

**Reference Values:**
FREE PROTOPORPHYRIN
<20 mcg/dL

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL

**Clinical References:**

**Protoporphyrins, Fractionation, Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the
severity and course of disease. EPP is caused by diminished ferrochelatase resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. XLDPP is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin in erythrocytes, and total protoporphyrin levels in plasma and feces. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PPFE / Protoporphyrins, Fractionation, Whole Blood -PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Evaluating patients with possible diagnoses of erythropoietic protoporphyria or X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
FREE PROTOPORPHYRIN
<20 mcg/dL

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL

**Clinical References:**

**PRTR**
Protriptyline (Vivactyl)

**Reference Values:**
Reference Range: 50 - 170 ng/mL

**PRSSZ**
PRSS1 Gene, Full Gene Analysis, Varies

**Clinical Information:** Hereditary pancreatitis (HP) is a rare autosomal dominant disorder associated with approximately 80% penetrance. HP is characterized by early onset acute pancreatitis during childhood or early adolescence. The acute pancreatitis in these patients generally progresses to chronic...
pancreatitis by adulthood and can eventually lead to both exocrine and endocrine pancreatic insufficiency. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%. Mutations in the protease serine 1 or cationic trypsinogen (PRSS1) gene are a common cause of HP. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis. PRSS1 mutations are infrequently found in patients with alcohol-induced and tropical pancreatitis. Although several mutations have been identified, the R122H, N29I and A16V mutations are the most common disease-causing mutations associated with HP. Data suggest that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Although these 3 alterations account for >90% of mutations detected in the cationic trypsinogen gene, the inability to identify mutations in approximately 20% of families with HP suggests the involvement of other loci or unidentified mutations in the cationic trypsinogen gene. Mutations in other genes, such as SPINK1, CFTR and CTRC have been associated with hereditary and familial pancreatitis. Abnormalities in these genes are not detected by this assay. However, genetic testing for these genes simultaneously, including PRSS1, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

**Useful For:** Confirmation of suspected clinical diagnosis of hereditary pancreatitis (HP) in patients with chronic pancreatitis Identification of familial PRSSI mutation to allow for predictive and diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**PCHE1**

**Pseudocholinesterase, Total, Serum**

**Clinical Information:** Serum cholinesterase, often called pseudocholinesterase (PCHE), is distinguished from acetylcholinesterase or "true cholinesterase," by both location and substrate. Acetylcholinesterase is found in erythrocytes, in the lungs and spleen, in nerve endings, and in the gray matter of the brain. It is responsible for the hydrolysis of acetylcholine released at the nerve endings to mediate transmission of the neural impulse across the synapse. PCHE, the serum enzyme, is also found in the liver, the pancreas, the heart, and in the white matter of the brain. Its biological role is unknown. The organophosphorus-containing insecticides are potent inhibitors of the true cholinesterase and also cause depression of PCHE. Low values of PCHE are also found in patients with liver disease. In general, patients with advanced cirrhosis and carcinoma with metastases will show a 50% to 70% decrease. Essentially normal values are seen in chronic hepatitis, mild cirrhosis, and obstructive jaundice. PCHE metabolizes the muscle relaxants succinylcholine and mivacurium, and therefore, alterations in PCHE will influence the physiologic effect of these drugs. In normal individuals (approximately 94% of the population) certain drugs and other agents, such as dibucaine and fluoride, will almost completely inhibit the PCHE activity. A small number of individuals (<1% of the
population) have been shown to have genetic variants of the enzyme, and therefore, cannot metabolize the muscle relaxants succinylcholine and mivacurium and experience prolonged apnea. These individuals generally have low levels of PCHE, which is not inhibited by dibucaine or fluoride. These individuals are either homozygotes or compound heterozygotes for an atypical gene controlling PCHE. Simple heterozygotes have also been identified who show intermediate enzyme values and inhibition.

**Useful For:** Monitoring exposure to organophosphorus insecticides Monitoring patients with liver disease, particularly those undergoing liver transplantation Identifying patients who are homozygous or heterozygous for an atypical gene and have low levels of pseudocholinesterase This test is not useful for the differential diagnosis of jaundice.

**Interpretation:** Patients with normal pseudocholinesterase (PCHE) activity show 70% to 90% inhibition by dibucaine, while patients homozygous for the abnormal allele show little or no inhibition (0%-20%) and usually low levels of enzyme. Heterozygous patients have intermediate PCHE levels and response to inhibitors. The atypical gene is inherited in an autosomal recessive pattern. In a positive patient, family members should be tested. Decreasing or low levels may indicate exposure to organophosphorus insecticides, as long as liver disease and an abnormal allele have been ruled out.

**Reference Values:**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>5320-12,920 U/L</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>0-15 years</td>
<td>5320-12,920 U/L</td>
</tr>
<tr>
<td>16-39 years</td>
<td>4260-11,250 U/L</td>
</tr>
<tr>
<td>40-41 years</td>
<td>5320-12,920 U/L</td>
</tr>
<tr>
<td>&gt; or =42 years: 5320-12,920 U/L</td>
<td></td>
</tr>
</tbody>
</table>

Note: Females age 18-41 years who are pregnant or taking hormonal contraceptives, the reference interval is 3650-9120 U/L.

**Clinical References:**

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**Psychosine, Blood Spot**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by an enzyme deficiency of galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide and lactosylsphingosine). Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows, with death usually occurring by age 2. Ten percent to 15% of individuals have late onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anytime from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed early, usually within the first 2 months of life. Psychosine is 1 of 4 substrates degraded by GALC and is a neurotoxin at elevated concentrations. Psychosine has been shown to be elevated in patients with symptomatic Krabbe disease or with saposin A cofactor deficiency and, therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or
absent GALC in leukocytes (CBGC / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with psychosine analysis can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR, Varies) allows for detection of the disease-causing variants in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease may have saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of the PSAP gene is useful in those with elevated psychosine and normal to reduced GALC activity with normal GALC sequencing.

**Useful For:** Aids in the biochemical diagnosis of Krabbe disease and saposin A cofactor deficiency Follow-up of individuals affected with Krabbe disease Follow-up testing after an abnormal newborn screening result for Krabbe disease This test is not capable of identifying carriers of Krabbe disease.

**Interpretation:** An interpretive report will be provided. An elevation of psychosine is indicative of symptomatic Krabbe disease or symptomatic saposin A cofactor deficiency.

**Reference Values:**
Normal <2 nmol/L psychosine

**Clinical References:**

**Psychosine, Spinal Fluid**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal disorder caused by deficient activity of the enzyme galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide, and lactosylsphingosine). Krabbe disease is caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 250,000 births. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows, with death usually occurring by 2 years of age. Ten percent to 15% of individuals have later onset variants of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression, presenting anytime from 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Psychosine (PSY) is a neurotoxin at elevated concentrations. Importantly, it is 1 of 4 substrates degraded by GALC. It has been shown to be elevated in patients with active Krabbe disease or with Saposin A cofactor deficiency, and therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent GALC in leukocytes (CBGC / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with psychosine analysis can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) allows for detection of the disease-causing mutations in affected patients and carrier detection in family members.
Individuals with a disease phenotype similar to Krabbe disease may have Saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of PSAP is useful in those with elevated psychosine and normal to reduced GALC activity with normal molecular genetic GALC analysis.

**Useful For:** Aids in the biochemical diagnosis of Krabbe disease using cerebrospinal fluid specimens
Follow-up of individuals affected with Krabbe disease Follow-up testing after an abnormal newborn screening result for Krabbe disease Monitoring of individuals at risk to develop late onset Krabbe disease Monitoring of individuals with Krabbe disease after hematopoietic stem cell transplantation

**Interpretation:** An elevation of psychosine is indicative of Krabbe disease or Saposin A cofactor deficiency.

**Reference Values:**
Normal < 0.04 nmol/L

**Clinical References:**

**Psychosine, Whole Blood**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal disorder caused by deficient activity of the enzyme galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide, and lactosylsphingosine). Krabbe disease is caused by alterations in the GALC gene, and it has an estimated frequency of 1 in 250,000 births. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows, with death usually occurring by 2 years of age. Ten percent to 15% of individuals have later onset variants of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression, presenting anytime from 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Psychosine (PSY) is a neurotoxin at elevated concentrations. Importantly, it is 1 of 4 substrates degraded by GALC. It has been shown to be elevated in patients with active Krabbe disease or with saposin A cofactor deficiency, and therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent GALC in leukocytes (GALCW / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with psychosine analysis can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR, Varies) allows for detection of the disease-causing alterations in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease may have saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of PSAP is useful in those with elevated psychosine and normal to moderately reduced GALC activity with normal molecular genetic GALC analysis.

Current as of June 14, 2021 12:13 pm CDT
**Useful For:** Aiding in the biochemical diagnosis of Krabbe disease using whole blood specimens

Follow-up of individuals affected with Krabbe disease

Follow-up testing after an abnormal newborn screening result for Krabbe disease

Monitoring of individuals at risk to develop late onset Krabbe disease

Monitoring of individuals with Krabbe disease after hematopoietic stem cell transplantation

**Interpretation:** An elevation of psychosine is indicative of Krabbe disease or saposin A cofactor deficiency.

**Reference Values:**

Normal <10 pmol/g Hb

**Clinical References:**


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**Psychotropic Pharmacogenomics Gene Panel, Varies**

**Clinical Information:** This panel provides a comprehensive analysis for multiple genes that have strong pharmacogenomic associations with medications used in the treatment of psychiatric disorders, including depression. Each sample is tested for specific variations with known functional impact.

Pharmacogenomic data for the following specific variants are reviewed and reported (if present):

- ADRA2A rs1800544
- ANKK1 (DRD2 associated) rs1800497
- CHRNA3 rs1051730
- COMT rs4680
- CYP1A2 *1F, *1K, *6, and *7
- EPHX1 rs2234922
- GRIK4 rs1954787
- HLA-A*31:01
- HTR2A rs7997012
- HTR2C rs3813929
- HTR2D rs1801131
- HTR3A rs1801133
- HTR3B rs1799971
- HTR3D rs3812718
- SLC6A4 linked polymorphic region (LPR)
- UGT2B15 rs1902023

Based on the results of each assay, a genotype is assigned and a phenotype is predicted for each gene. Assessment of multiple genes may assist the ordering clinician with personalized drug recommendations, avoidance of adverse drug reactions, and optimization of drug treatment.

**Useful For:** Individualizing selection and dosage of medications prescribed for treatment of depression and other psychiatric disorders based on genetic variation Identifying genetic variation in genes known to be associated with response and/or risk of toxicity with psychotropic medications Evaluating patients who have failed therapy with selective serotonin reuptake inhibitors (SSRI)

Evaluating patients with treatment-resistant depression Predicting response time to improvement with SSRI

**Interpretation:** An interpretive report will be provided that focuses on medications and genes with published pharmacogenomic practice guidance by the Clinical Pharmacogenetics Implementation Consortium or other professional organizations (1-3), where strong FDA guidance has been issued in drug labels, (4) or where peer-reviewed literature strongly suggests that assessment of pharmacogenomic variants may enhance patient care. (5-8) For additional information regarding...
pharmacogenomic genes and their associated medications, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.


PT-Fibrinogen, Plasma

Clinical Information: Fibrinogen, also known as factor 1, is a plasma protein that can be transformed by thrombin into a fibrin gel ("the clot"). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely than the acquired to be associated with bleeding or thrombotic disorders. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Congenital dysfibrinogenemias usually are inherited as autosomal codominant traits. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or renal diseases associated with elevated fibrinogen levels. Fibrinogen is an acute-phase reactant, so a number of acquired conditions can result in an increase in its plasma level: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial and venous thromboembolism.

Useful For: Detecting increased or decreased fibrinogen (factor 1) concentration of acquired or congenital origin Differentiating hypofibrinogenemia from dysfibrinogenemia

Interpretation: This test assesses the level of total clottable fibrinogen (see Cautions).

Reference Values: Only orderable as part of a coagulation reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
**PTENZ**

**PTEN Gene, Full Gene Analysis, Varies**

**Clinical Information:** Germline variants in the PTEN gene are associated with a rare collection of clinical syndromes referred to as PTEN hamartoma tumor syndrome (PHTS). This includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS) and Proteus-like syndrome (PLS). Although each of these syndromes has its own unique features, all 4 appear to be associated with multiple hamartomatous lesions, vascular lesions, and macrocephaly. Affected individuals have an increased risk of cancer, including cancers of the breast, endometrium, thyroid, colon, and kidney. PHTS is an autosomal dominant disorder and penetrance is believed to be quite high. CS is a multiple hamartoma syndrome associated with trichilemmomas, mucocutaneous papillomatous papules, and macrocephaly. Affected individuals are at an increased risk for breast, thyroid, and endometrial carcinoma. BRRS is characterized by macrocephaly, intestinal hamartomas, lipomatosis, hemangiomatosis, and pigmented macules on the glans penis. PS is associated with congenital malformations, overgrowth, macrocephaly, hyperostosis, connective tissue nevi, and epidermal nevi. PLS refers to individuals who have features of PS, but do not meet diagnostic criteria.

**Useful For:** Confirming a diagnosis of PTEN hamartoma tumor syndrome, which includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, or Proteus-like syndrome. Identifying variants in the PTEN gene

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
**PU1 Immunostain, Technical Component Only**

**Clinical Information:** PU.1 is an erythroblast transformation specific (ETS) family transcription factor that regulates expression of immunoglobulin genes and other genes important in B-cell development. The nuclear protein is expressed in B cells in the germinal center and mantle zone. It is not expressed in plasma cells. PU.1 also plays a role in the differentiation of myeloid cells and is expressed in macrophages (strong staining), mast cells, early erythroid cells, and megakaryocytes. Expression of BOB.1, OCT-2, and PU.1 transcription factors are often downregulated in classical Hodgkin lymphoma. This property can be useful in lymphoma diagnosis.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**PUSE Pumpkin Seed, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing the diagnosis of an allergy to pumpkin seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

(DPD) deficiency can result in a severe disorder in infancy involving seizures, intellectual disability, microcephaly and hypertonia. In its mildest form however, individuals with DPD deficiency may be asymptomatic but are at risk for life-threatening toxic reactions to a certain class of drugs used to treat cancer called fluoropyrimidines (eg, 5-fluorouracil and capecitabine). If individuals with DPD deficiency ingest this medication, they can develop fluoropyrimidine toxicity. This drug toxicity can result in inflammation of the gastrointestinal tract and associated symptoms, as well as abnormal blood counts including neutropenia and thrombocytopenia.

**Useful For:** Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory evaluation of primary and secondary hyperuricemias Assessing tolerance for fluoropyrimidine drugs used in cancer treatment Aiding in the diagnosis of individuals with suspected dihydropyrimidine dehydrogenase (DPD) deficiency

**Interpretation:** Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies, and a phone number of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reference Values</th>
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<tr>
<td>Purines and Pyrimidines</td>
<td></td>
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<tr>
<td>Age range</td>
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**Purines and Pyrimidines Panel, Urine**

**Clinical Information:** Purines (adenine, guanine, xanthine, hypoxanthine) and pyrimidines (uracil, thymine, cytosine, orotic acid) are involved in all biological processes, providing the basis for storage, transcription, and translation of genetic information as RNA and DNA. Purines are required by all cells for growth and survival and also play a role in signal transduction and translation. Purines and pyrimidines originate primarily from endogenous synthesis, with dietary sources playing only a minor role. The end product of purine metabolism is uric acid (2,6,8-trioxypurine), which must be excreted continuously to avoid toxic accumulation. Disorders of purine and pyrimidine metabolism can involve all organ systems at any age. The diagnosis of the specific disorders of purine and pyrimidine metabolism is based upon the clinical presentation of the patient, determination of specific concentration patterns of purine and pyrimidine metabolites, and confirmatory enzyme assays and molecular genetic testing. Numerous inborn errors of purine and pyrimidine metabolism have been documented. Clinical features are dependent upon the specific disorder but represent a broad spectrum of manifestations that may include immunodeficiency, developmental delay, nephropathy, and neurologic involvement. The most commonly described disorder of purine metabolism involves a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT) which causes 3 overlapping clinical syndromes depending on the amount of residual enzyme activity. The majority of patients with HPRT deficiency have classic Lesch-Nyhan syndrome, a severe -X-linked disorder characterized by crystals in urine, neurologic impairment, mild to severe intellectual disability, development of self-injurious behavior, and uric acid nephropathy. Treatments for Lesch-Nyhan syndrome include allopurinol, urine alkalinization and hydration for nephropathy, and supportive management of neurologic symptoms. For milder forms of HPRT deficiency, treatment that can mitigate the potentially devastating effects of these diseases are disorder dependent; therefore, early recognition through screening and subsequent confirmatory testing is highly desirable. Urine s-sulfocysteine is elevated in 2 disorders with similar clinical phenotypes: molybdenum cofactor deficiency (MoCD) and isolated sulfite oxidase deficiency. Molybdenum is an important trace element that is biosynthesized into an important cofactor, which is essential for the proper functioning of the enzymes xanthine oxidase, sulfite oxidase, and aldehyde oxidase in addition to nitrogenases and nitrate reductase. Four genes are important in mediating the biosynthetic pathway to create molybdenum cofactor: MOCS1, MOCS2, MOCS3, and GPHN (gephyrin). The 3 clinical types of MoCD are autosomal recessive diseases resulting from 2 pathogenic variants in the respective causative gene. MoCDs result in a progressive neurodegenerative disease that manifests with seizures and brain abnormalities in the first weeks to months of life. The most common type of MoCD is MoCD A, caused by variants in MOCS1 and resulting in neonatal or infantile onset seizures and postnatal encephalopathy with rapidly progressive neurodegeneration. Infants with MoCD B (MOCS2 or MOCS3), and C (GPHN) have all been reported but are rare. Infants with MoCD have increased s-sulfocysteine and hypoxanthine and decreased uric acid concentrations in urine. Treatment for MoCD A only is available via clinical trial with cyclic pyranopterin monophosphate infusion and is most effective when initiated early. Isolated sulfite oxidase deficiency (ISOD) is an autosomal recessive disorder caused by deficiency of the enzyme sulfite oxidase, which results in progressive neurodegenerative disease in most cases. ISOD is the result of pathogenic variants in the SUOX gene. ISOD is a spectrum of disease ranging from severe, early onset disease that appears in the first days of life with seizures, feeding issues, and neurologic issues causing abnormal muscle tone, to mild, later onset disease manifesting after 6 months of age with developmental delay or regression, movement issues, which can be episodic, and ectopia lentis in some cases. Infants with ISOD have increased s-sulfocysteine and normal hypoxanthine concentrations in urine. Treatment is largely symptomatic, with medication for seizures and movement/neurologic issues. Unfortunately, no treatment for the underlying metabolic defect is currently available. Prevalence is unknown, but ISOD is likely underdiagnosed. Hereditary xanthinuria results in renal stones and, less commonly, muscle pain and cramping caused by accumulation of xanthine that forms crystals in the kidneys and muscle tissue. There are 2 types of hereditary xanthinuria: type I caused by deficiency of xanthine dehydrogenase resulting from pathogenic variants in the XDH gene, and type II caused by...
deficiency of molybdenum cofactor sulfurase resulting from variants in the MOCOS gene. Individuals
with xanthinuria have increased xanthine and decreased uric acid concentrations in urine. The incidence
of both types of hereditary xanthinuria is about 1 in 69,000 individuals.

**Useful For:** Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine
metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory
evaluation of primary and secondary hyperuricemias

**Interpretation:** Abnormal concentrations of measurable compounds will be reported along with an
interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results
and of their significance, a correlation to available clinical information, possible differential diagnosis,
recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular
analysis), name, and phone number of contacts who may provide these studies, and a phone number of the
laboratory directors in case the referring physician has additional questions.

**Reference Values:**

Purines and pyrimidines panel reference values (all results reported as mmol/mol creatinine)

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FPYRE
57540
Pyrethrum IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Åæ, 0.69 Low Positive 2 0.70 Åæ, 3.49 Moderate Positive 3 3.50 Åæ, 17.49 Positive 4 17.50 Åæ, 49.99 Strong Positive 5 50.00 Åæ, 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FPYD
90281
Pyridostigmine, Serum/Plasma

Reference Values:
Reporting limit determined each analysis
Synonym(s): Mestinon

- 30-125 ng/mL plasma in myasthenia gravis patients restores normal neuronal transmission.
- Specimens must be kept frozen.

FP5PC
75216
Pyridoxal 5-phosphate (CSF)

Reference Values:
30-80 nmol/L 0 to <3 months
23-65 nmol/L 3 months to <1 years
15-51 nmol/L 1 year to <4 years
10-37 nmol/L 4 years to adult

PLP
42359
Pyridoxal 5-Phosphate (PLP), Plasma

Clinical Information: Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5'-phosphate esters. Due to its role as a cofactor in a number of enzymatic reactions, pyridoxal phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid are observed in cases of hypophosphatemia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

Useful For: Determining vitamin B6 status, including in persons who present with progressive nerve compression disorders, such as carpal tunnel and tarsal tunnel syndromes Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatemia

Interpretation: Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid
(PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results: If PLP is greater than 100 mcg/L; or -If PLP is greater than 100 mcg/L and PA is less than or equal to 30, the increased pyridoxal 5-phosphate is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is greater than 100 mcg/L and PA is 31 to 100 mcg/L; or PLP is 81 to 100 mcg/L and PA is less than or equal to 30 mcg/L, the increased pyridoxal 5-phosphate is likely related to dietary supplementation; however a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is greater than 30; or PLP is greater than 100 mcg/L and PA is greater than 100 mcg/L, the elevated pyridoxal 5-phosphate is likely due to dietary supplementation.

Reference Values:
5-50 mcg/L


B6PA
Pyridoxic Acid (PA), Plasma
Reference Values:
Only orderable as part of a profile. For more information see B6PRO / Vitamin B6 Profile (PLP and PA), Plasma.

P5NT
Pyrimidine 5' Nucleotidase, Blood
Clinical Information: Pyrimidine 5' nucleotidases (P5'Ns) are catabolic enzymes that regulate cellular nucleotide and nucleoside levels through the dephosphorylation of noncyclic nucleoside 5â€™-monophosphates. P5â€™N activity is much higher in reticulocytes than in aged red cells due to increased demand during erythroid maturation. Reticulocyte ribosomal RNA degradation results in pyrimidine nucleotide residues that require conversion to nucleosides to allow diffusion outside the cell. Disruption of this process results in intracellular pyrimidine nucleotide accumulation visible as coarse basophilic stippling. Several different 5'-nucleotidase (5â€™NT) enzymes have been identified with distinctive substrate specificity, cellular localization, and tissue distribution. Only P5â€™NT type 1 is known to be associated with P5'N deficiency (also called uridine 5' monophosphate hydrolase deficiency), a cause of congenital nonspherocytic hemolytic anemia (OMIM 266120, autosomal recessive). The disorder manifests as mild/compensated to moderate hemolytic anemia with persistent reticulocytosis. Additional features include jaundice/neonatal hyperbilirubinemia, splenomegaly, and characteristic marked basophilic stippling on the peripheral blood smear. Coincident hemoglobin E (Hb E) may lead to a more severe hemolytic anemia. P5'N deficiency is caused by homozygous or compound heterozygous alterations in the NT5C3A gene, mapped to chromosome 7p14. Assaying for the presence of pyrimidine nucleotides serves as a surrogate marker for P5'N deficiency and is not specific for a diagnosis of hereditary P5â€™NT deficiency. Enzyme function is magnesium ion-dependent and is inhibited by metal chelating reagents, such as EDTA. Activity is inhibited by heavy metal ions including lead, mercury, copper, nickel, and cadmium, and toxic levels can cause accumulation of intracellular pyrimidine nucleotides.

Useful For: Evaluation of marked basophilic stippling Evaluation of hemolytic anemia
**Interpretation:** A normal result indicates the absence of pyrimidine nucleotides and indicates normal pyrimidine 5′ nucleotidase (P5′N) function. An abnormal result (abnormal spectral scan) indicates the presence of pyrimidine nucleotides and possible P5′N deficiency. Enzyme activity is inhibited by heavy metal ions including lead, mercury, copper, nickel, and cadmium. Toxic levels can cause accumulation of intracellular pyrimidine nucleotides. If results are abnormal clinical correlation is recommended to exclude heavy metal poisoning.

**Reference Values:**

Normal

**Clinical References:**

**Pyruvate Dehydrogenase Complex, Fibroblasts**

**Clinical Information:** The pyruvate dehydrogenase (PDH) complex (PDHC) catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, a critical step in the production of cellular energy. PDHC is a multienzyme complex located in the inner mitochondrial membrane consisting of 6 different components: pyruvate dehydrogenase (E1, with alpha and beta subunits), dihydriolipoic transacetylase (E2), dihydriolipoyl dehydrogenase (E3), 2 regulatory enzymes (PDH kinase and PDH phosphatase), and E3-binding protein. PDHC deficiency is a mitochondrial disorder with a variable clinical presentation ranging from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. In infants and children with PDHC deficiency, the most common features are delayed development and hypotonia, as well as acquired microcephaly. Seizures and ataxia are also frequent features. Less common manifestations include congenital brain malformations, particularly ventriculomegaly and agenesis of the corpus callosum, or degenerative changes including Leigh disease. Facial dysmorphism is seen in a small portion of patients. PDHC deficiency is one of the most common causes of primary lactic acidosis in children. The severity of the disease progression is thought to be related to the severity of the lactic acidosis as well as the level of residual enzyme activity. PDHC deficiency can be caused by defects in the E1 alpha, E1 beta, E2, or E3 subunits. The most common cause of PDHC deficiency is a defect in the E1 alpha subunit, which is encoded by the PDH1 gene located on the X chromosome. Both females and males with a PDH1 gene mutation are affected with PDHC deficiency; thus, it is classified as X-linked dominant. Mutations in the PDH1 gene are typically de novo. A major cause of primary lactic acidosis in children is PDHC deficiency; therefore, it should be suspected when blood and cerebrospinal fluid (CSF) lactate and pyruvate is elevated and the lactate-to-pyruvate (L:P) ratio is normal or slightly elevated. Plasma or CSF alanine (AAQP / Amino Acids, Quantitative, Plasma or AACSF / Amino Acids, Quantitative, Spinal Fluid) may also be increased. A diagnosis of PDHC deficiency depends on the measurement of enzyme activity in cells or tissues, most commonly in skin fibroblasts.

**Useful For:** Evaluation of patients with a clinical suspicion of a pyruvate dehydrogenase complex deficiency or an energy metabolism disorder

**Interpretation:** When below-normal enzyme activities are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

**Reference Values:**

>25.00 nmol/min/g protein (Normal)
PK1
607459

Pyruvate Kinase Enzyme Activity, Blood

Clinical Information: Deficiencies of most of the enzymes of the Embden-Meyerhof (glycolytic) pathway, including pyruvate kinase (PK), have been reported. PK deficiency (OMIM 266200) is the erythrocyte enzyme deficiency most frequently found to be a cause of chronic nonspherocytic hemolytic anemia (CNSHA). It is an autosomal recessive disorder and parents of affected patients are typically carriers. Some PK carrier states can exacerbate other RBC disorders (ie, coincident glucose 6-phosphate dehydrogenase deficiency or hemoglobin S trait).

PK1

> Reference values apply to all ages.


Useful For: Evaluation of nonspherocytic hemolytic anemia Evaluation of neonatal anemia or jaundice Evaluation of unexplained noninfectious hepatic failure Evaluation of unexplained iron overload Evaluation of unusually severe hemoglobin S trait Evaluation of unusually severe glucose 6-phosphate dehydrogenase deficiency Investigating families with pyruvate kinase deficiency to determine inheritance pattern and for genetic counseling

Interpretation: Pyruvate kinase (PK) deficiency is the most easily masked of the RBC enzyme disorders and can be difficult to classify without complete information, which may require comparison to other RBC enzyme activity levels or correlation with results of PKLR gene molecular testing (PKLRG / Pyruvate Kinase Liver and Red Blood Cell [PKLR] Full Gene Sequencing and Large Deletion Detection, Varies). Most hemolytic anemias due to PK deficiency are associated with activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which paradoxically may occur in individuals with the most severe symptoms. Isolated carriers (heterozygotes) may show mildly decreased activity and are typically hematologically normal, although the carrier state may exacerbate other RBC disorders such as glucose 6-phosphate dehydrogenase deficiency, RBC membrane disorders, or hemoglobinopathies. Some alterations in other genes (ie, KLF1) can be associated with decreased PK levels. Elevated PK concentrations can be found in those patients with younger erythrocyte population. This may be due to the patient being a newborn or young red cells are being produced in response to the anemia (reticulocytosis).
Rare PK deficient cases have been associated with minimally increased PK levels; however, comparison to other RBC enzyme activity would be critical in these cases for accurate interpretation.

Reference Values:
> or =12 months of age: 5.5-12.4 U/g Hb

Reference values have not been established for patients who are less than 12 months of age.

Clinical References:

**PKC**

608418

**Pyruvate Kinase Enzyme Activity, Blood**

**Clinical Information:** Deficiencies of most of the enzymes of the Embden-Meyerhof (glycolytic) pathway, including pyruvate kinase (PK), have been reported. PK deficiency (OMIM 266200), is the erythrocyte enzyme deficiency most frequently found to be a cause of chronic nonspherocytic hemolytic anemia (CNSHA). It is an autosomal recessive disorder and parents of affected patients are typically carriers. Some PK carrier states can exacerbate other red blood cell disorders (ie, coincident glucose 6-phosphate dehydrogenase deficiency or hemoglobin S trait). Clinically significant PK deficiency manifests in widely variable severity ranging from incidental compensated mild normocytic anemia to severe anemia. Neonatal jaundice is very common, and a significant subset of neonates has perinatal complications. Other symptoms include early gallstones and splenomegaly. Iron overload, even in the absence of frequent transfusions, is very common. Rare severe PK deficiency is associated with hydrops fetalis/fetal demise or unexplained non-infectious hepatic failure. Acquired PK deficiency can arise secondary to myeloid neoplasms.

**Useful For:** Evaluation of nonspherocytic hemolytic anemia Evaluation of neonatal anemia or jaundice Evaluation of unexplained non-infectious hepatic failure Evaluation of unexplained iron overload Evaluation of unusually severe hemoglobin S trait Evaluation of unusually severe glucose-6-phosphate dehydrogenase deficiency Investigating families with pyruvate kinase deficiency to determine inheritance pattern and for genetic counseling

**Interpretation:** Pyruvate kinase (PK) deficiency is the most easily masked of the red blood cell (RBC) enzyme disorders and can be difficult to classify without complete information, which may require comparison to other RBC enzyme activity levels and/or correlation with results of PKLR gene molecular testing (PKLRG / Pyruvate Kinase Liver and Red Blood Cell (PKLR), Full Gene Sequencing and Large Deletion Detection, Varies). Most hemolytic anemias due to PK deficiency are associated with activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which, paradoxically, may occur in individuals with the most severe symptoms. Isolated carriers (heterozygotes) may show mildly decreased activity and are typically hematologically normal, although the carrier state may exacerbate other RBC disorders such as glucose 6-phosphate dehydrogenase (G6PD), deficiency, RBC membrane disorders or hemoglobinopathies. Some alterations in other genes (ie, KLF1) can be associated with decreased PK levels. Elevated PK concentrations can be found in those patients with younger erythrocyte population. This may be due to the patient being a newborn or young red cells are being produced in response to the anemia (reticulocytosis). Rare PK deficient cases have been associated with minimally increased PK levels; however, comparison to other RBC enzyme activity would be critical in these cases for accurate interpretation.

**Reference Values:**
Only available as part of a profile. For more information see:
HAEV1 / Hemolytic Anemia Evaluation, Blood
EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood
> or =12 months of age: 5.5-12.4 U/g Hb
Reference values have not been established for patients who are less than 12 months of age.


PKLRG 64564 Pyruvate Kinase Liver and Red Blood Cell (PKLR), Full Gene Sequencing and Large Deletion Detection, Varies

Clinical Information: The glycolytic pathway is used by all tissues for energy production through the formation of adenosine triphosphate (ATP). It is particularly important in red blood cells, which are dependent upon this pathway for energy due to their lack of mitochondria. The PKLR gene encodes for pyruvate kinase, the rate-limiting glycolytic enzyme that catalyzes the transphosphorylation from phosphoenolpyruvate (PEP) to adenosine diphosphate (ADP) creating pyruvate and ATP. Pyruvate kinase (PK) deficiency is a relatively common cause of hereditary nonspherocytic hemolytic anemia,(1) with an estimated prevalence of 1:20,000 among people of European descent. The severity of hemolysis varies from fully compensated forms to life-threatening neonatal anemia requiring transfusions.(2) Over 200 different variants have been reported in the PKLR gene. Most are single nucleotide substitutions although rarer large deletions have also been identified. PK deficiency is inherited in an autosomal recessive manner, and genetic results should be correlated with enzyme levels performed remote from transfusion when possible. PK deficiency can be difficult to interpret based on enzyme level alone and may be only mildly decreased or normal in those with the most severe symptoms or after splenectomy due to reticulocytosis.(2) Comparison to other erythrocyte enzyme levels is usually very helpful in this regard. Heterozygous carriers of PKLR variants have intermediate enzyme levels and are not symptomatic.

Useful For: Aid in the diagnosis of pyruvate kinase (PK) deficiency Ascertain a causative variant in the PKLR gene of patients with low or relatively low levels of erythrocytic PK enzymatic activity Ascertain carrier status of family members of individuals diagnosed with PK deficiency for genetic counseling purposes

Interpretation: All detected alterations will be evaluated according to current ACMG recommendations.(3) Variants will be classified based on known, predicted, or possible effect on gene pathogenicity and reported with interpretive comments detailing their potential or known clinical significance.

Reference Values:
An interpretive report will be provided.

**Pyruvate, Spinal Fluid**

**Clinical Information:** Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though pyruvate is not diagnostic in itself, analysis with lactate has diagnostic value as many inborn errors of metabolism present with laboratory findings that include lactic acidosis and/or a high lactate:pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and the L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

**Useful For:** Investigating possible disorders of mitochondrial metabolism, when used in conjunction with cerebrospinal fluid lactate, collected at the same time, to determine the lactate-to-pyruvate (L:P) ratio Evaluating patients with neurologic dysfunction and normal blood L:P ratios

**Interpretation:** An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found in acutely ill patients.

**Reference Values:**
0.06-0.19 mmol/L

**Clinical References:**

**Pyruvic Acid, Blood**

**Clinical Information:** Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though isolated elevated pyruvate is not diagnostic of any inborn error of metabolism, analysis with lactate may suggest an inborn error of metabolism as some present with lactic acidosis or a high lactate-to-pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and...
myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels, though further confirmatory testing will be required to establish a diagnosis. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

**Useful For:** Screening for possible disorders of mitochondrial metabolism, when used in conjunction with blood lactate collected at the same time, to determine the lactate-to-pyruvate ratio.

**Interpretation:** An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found if the patient is acutely ill. Cerebrospinal fluid (CSF) L:P ratio may assist in evaluation of patients with neurologic dysfunction and normal blood L:P ratios. Blood and CSF specimens should be collected at the same time.

**Reference Values:**
- NIH Unit: 0.08-0.16 mmol/L
- 0.7-1.4 mg/dL

**Clinical References:**
II titers generally equal to or greater than phase I titers. Titers seen in Q fever endocarditis are similar in magnitude, although the phase I titers are quite often higher than the phase II titers.

**Useful For:** Diagnosing Q fever

**Interpretation:** Phase I antibody titers greater than or equal to phase II antibody titers are consistent with chronic infection or convalescent phase Q fever. Phase II antibody titers greater than or equal to phase I antibody titers are consistent with acute/active infection. A negative result argues against Coxiella burnetii infection. If early acute Q fever infection is suspected, collect a second specimen 2 to 3 weeks later and retest. In Q fever sera, it is common to see IgG titers of 1:128 or greater to both phase I and phase II antibody titers. IgG class antibody titers appear very early in the disease, reaching maximum phase II titers by week 8 and persisting at elevated titers for longer than a year. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence. In Q fever sera, it is common to see IgM titers of 1:64 or greater. IgM class antibody titers appear very early in the disease, reaching maximum phase II titers by week 3 and declining to very low levels by week 14. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence.

**Reference Values:**

- **Q FEVER PHASE I ANTIBODY, IgG**
  
  <1:16

- **Q FEVER PHASE II ANTIBODY, IgG**
  
  <1:16

- **Q FEVER PHASE I ANTIBODY, IgM**
  
  <1:16

- **Q FEVER PHASE II ANTIBODY, IgM**
  
  <1:16

Reference values apply to all ages.

**Clinical References:**


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**Quad Screen (Second Trimester) Maternal, Serum**

**Clinical Information:** Maternal serum screening is used to identify pregnancies that may have an increased risk for certain birth defects, including neural tube defects (NTD), trisomy 21 (Down syndrome), and trisomy 18 (Edwards syndrome). The screen is performed by measuring analytes in maternal serum that are produced by the fetus and the placenta. The analyte values along with maternal demographic information such as age, weight, gestational age, diabetic status, and race are combined in a mathematical model to derive a risk estimate. A specific cutoff for each condition is used to classify the risk estimate as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis but rather indicates that further evaluation should be considered. Analytes: Alpha-Fetoprotein (AFP)

Alpha-fetoprotein (AFP) is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from a non-pregnancy level of 0.2 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open NTD, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing
elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal distress situations (eg, threatened abortion and fetal demise) also may result in maternal serum AFP elevations. Increased maternal serum AFP concentrations also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP concentrations have been associated with an increased risk for genetic conditions such as trisomy 21 and trisomy 18. Estriol (uE3) Estriol, the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the intact feto-placental unit. Estriol exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of unconjugated estriol in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates estriol to make it more water soluble for urinary excretion. Estriol levels increase during the course of pregnancy. Decreased unconjugated estriol has been shown to be a marker for trisomy 21 and trisomy 18. Low levels of estriol also have been associated with pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Human Chorionic Gonadotropin (Total Beta-hCG: ThCG) Human chorionic gonadotropin (hCG) is a glycoprotein consisting of 2 non-covalently bound subunits. The alpha subunit is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyrotropin (formerly thyroid-stimulating hormone; TSH), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. hCG is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum, and hence, progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with trisomy 21, while decreased levels may be seen in trisomy 18. Elevations of hCG also can be seen in multiple pregnancies, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetalis. Inhibit A Inhibins are a family of heterodimeric glycoproteins, primarily secreted by ovarian granulosa cells and testicular Sertoli cells, which consist of disulfide-linked alpha and beta subunits. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta A or a beta B chain, they are designated as inhibit A or inhibit B, respectively. Together with the related activins, which are homodimers or heterodimers of beta A and B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the feto-placental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibit A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibit A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibit A levels are typically higher in trisomy 21 pregnancies). However, despite their similar behavior, measuring maternal serum inhibit A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for trisomy 21.

**Useful For:** Prenatal screening for open neural tube defect (alpha-fetoprotein only), trisomy 21 (alpha-fetoprotein, human chorionic gonadotropin, estriol, and inhibit A) and trisomy 18 (alpha-fetoprotein, human chorionic gonadotropin, and estriol)

**Interpretation:** Neural Tube Defects (NTD) A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of neural tube defects (NTD). A screen-positive result indicates that the calculated AFP MoM is 2.50 or greater and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual's pretest risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of NTD but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with NTD have elevated AFP, MoM values greater than 2.5. Trisomy 21 (Down syndrome) and Trisomy 18 (Edwards syndrome): A screen-negative result indicates that the calculated screen risk is below the established cutoff of 1/270 for trisomy 21 and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 21 or trisomy 18. When a trisomy 21 second-trimester risk cutoff of 1/270 is used
for follow-up, the combination of maternal age, AFP, estriol, human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 77% to 81% with a false-positive rate of 6% to 7%. In practice, both the detection rate and false-positive rate increase with age. The detection rate ranges from 66% (early teens) to 99% (late 40s), with false-positive rates of between 3% and 62%, respectively. The detection rate for trisomy 18 is 60% to 80% using a second trimester cutoff of 1/100. Follow-up
Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (maternal date of birth, gestational dating, etc). If any information is incorrect, the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD or trisomy 21 screen-positive results. Many pregnancies affected with trisomy 18 are small for gestational age. Recalculations that lower the gestational age may decrease the detection rate for trisomy 18. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTD) are typically offered.

Reference Values:
NEURAL TUBE DEFECTS
An AFP multiple of the median (MoM) <2.5 is reported as screen negative. AFP MoMs > or =2.5 (singleton and twin pregnancies) are reported as screen positive.

DOWN SYNDROME
Calculated screen risks <1/270 are reported as screen negative, risks > or =1/270 are reported as screen positive.

TRISOMY 18
Calculated screen risks <1/100 are reported as screen negative, risks > or =1/100 are reported as screen positive.

An interpretive report will be provided.


QuantiFERON-TB Gold Plus, Blood
Clinical Information: Latent tuberculosis infection (LTBI) is a non-communicable, asymptomatic condition that persists for many years in individuals and may progress to active tuberculosis disease, particularly in immunosuppressed patients. The primary goal for diagnosis of LTBI is to initiate medical treatment in order to prevent progression to active disease. Historically, detection of LTBI has been done using the tuberculin skin test (TST). The TST has certain limitations, however, including subjective interpretation, limited sensitivity in immunosuppressed patients, and the possibility of false-positive results in individuals who have received the bacille Calmette-Guerin (BCG) vaccine or are infected with other mycobacteria. The QuantiFERON-TB Gold Plus (QFT-Plus) test is an interferon (IFN)-gamma release assay (IGRA) that assesses the cell-mediated immune response to 2 Mycobacterium tuberculosis complex antigens, ESAT-6 and CFP-10, by measuring IFN-gamma levels
in plasma. These 2 proteins are absent from all bacille Calmet-Guerin (BCG) strains and from most non-tuberculosis mycobacteria with the exception of Mycobacterium kansasii, Mycobacterium szulgai, and Mycobacterium marinum. Individuals infected with M tuberculosis complex agents, including M tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti, Mycobacterium caprae, and Mycobacterium canetti, usually have lymphocytes in their blood that recognize these specific antigens and this recognition leads to the generation and secretion of IFN-gamma. This cytokine is subsequently detected and quantified using an IFN-gamma enzyme-linked immunosorbent assay. In an M tuberculosis infection, CD4+ T cells play a critical role in immunological control through secretion of IFN-gamma. The prior version of the QFT-Plus assay, the QuantiFERON-TB Gold In-Tube (QFT-Gold) assay, only detected IFN-gamma secreted from CD4+ T cells. Evidence now supports a role for CD8+ T cells in host defense against M tuberculosis infection by likewise producing IFN-gamma, but also by stimulating macrophages to suppress the growth of M tuberculosis, to kill infected cells, and to directly lyse intracellular M tuberculosis bacteria. IFN-gamma-producing M tuberculosis specific CD8+ T cells have been detected in subjects with LTBI and in patients with active TB. ESAT-6 and CFP-10 specific CD8+ T cells have also been more frequently described in patients with active tuberculosis (TB) versus patients with LTBI, and have been detected in HIV-positive patients and children with TB disease. The QFT-Plus assay has 2 distinct TB antigen tubes: TB Antigen Tube 1 (TB1) and TB Antigen Tube 2 (TB2). Both tubes contain peptide antigens from ESAT-6 and CFP-10 for stimulation of a CD4+ T-cell IFN-gamma response. However, the TB2 tube also contains an additional set of ESAT-6 and CFP-10 peptides specifically designed to stimulate a CD8+ T-cell response. For the most up-to-date information regarding use of IGRAs, refer to the most recent guidelines on the Diagnosis of Tuberculosis in Adults and Children from the American Thoracic Society, the Infectious Diseases Society of America, the Centers for Disease Control and Prevention.(1)

**Useful For:** Indirect test for Mycobacterium tuberculosis infection, to be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations This test is not recommended for use for diagnosis of active tuberculosis (TB) infection.

**Interpretation:** A single positive result by this test should not be used solely to diagnose latent tuberculosis (TB). Results should be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations. Positive: Interferon-gamma (IFN-gamma) response to Mycobacterium tuberculosis antigens detected, suggesting infection with M tuberculosis. Positive results in patients at low-risk for TB should be interpreted with caution and repeat testing on a new sample should be considered as recommended by the 2017 American Thoracic Society, the Infectious Diseases Society of America, the Centers for Disease Control and Prevention (ATS/IDSA/CDC) Clinical Practice Guidelines for Diagnosis of Tuberculosis in Adults and Children.(1) False-positive results may occur in patients with prior infection with Mycobacterium marinum, Mycobacterium szulgai, or Mycobacterium kansasii. Negative: No IFN-gamma response to M tuberculosis antigens was detected. Latent infection with M tuberculosis is unlikely. A single negative result does not exclude infection with M tuberculosis. In patients at high risk for M tuberculosis infection, a second test should be considered in accordance with the 2017 ATS/IDSA/CDC Clinical Practice Guidelines for Diagnosis of Tuberculosis in Adults and Children.(1) Indeterminate due to Low Mitogen Value: Indeterminate results due to a low IFN-gamma level in the mitogen (positive control) tube. This may occur due to a low lymphocyte count, reduced lymphocyte activity, or inability of the patient’s lymphocytes to generate IFN-gamma. Indeterminate due to High Nil value: Indeterminate results due to a high level of IFN-gamma in the Nil (negative control) tube. This may occur due to heterophile antibody effects or nonspecific, circulating IFN-gamma in the patient’s blood sample. Repeat testing on a new specimen is suggested.

**Reference Values:** Negative

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/ml) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of one or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression of CD19, while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3, CD4, CD8), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes inpatients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency (SCID) and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of Chronic Lymphocytic Leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia recommends changing the diagnostic criteria for CLL from an absolute lymphocyte count (ALC) greater than 5 x 10^9/L to a circulating B-cell count greater than 5 x 10^9/L previously defined in the 1996 National Cancer Institute (NCI) guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

Useful For: Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

Interpretation: When the CD4 count falls below 500 cells/ml, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/ml, prophylaxis against Pneumocystis jiroveci pneumonia is recommended.
Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References:

Queen Palm, IgE, Serum

Clinical Information:
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For:
Establishing a diagnosis of an allergy to queen palm Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation:
Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Quetiapine (Seroquel)

Reference Values:
Units: ng/mL

Therapeutic and toxic ranges have not been established. Expected steady-state Quetiapine plasma levels in patients receiving recommended daily dosages: 100 - 1000 ng/mL.

Quinidine, Serum

Clinical Information: Quinidine is indicated for atrial fibrillation and flutter, and life-threatening ventricular arrhythmia. Optimal serum concentrations are in the range of 2.0 to 5.0 mcg/mL, with toxicity apparent at levels of 6.0 mcg/mL or higher. Symptoms of toxicity (cinchonism) include tinnitus, light-headedness, premature ventricular contractions, and atrioventricular block. Gastrointestinal distress is a frequent side effect that becomes more severe and is associated with nausea and vomiting at higher drug concentrations. The half-life of quinidine is 6 to 8 hours. Physiologic processes that generally reduce hepatic metabolism and renal clearance increase serum quinidine levels, while comedication with cytochrome p450 (CYP)-enzyme inducers enhances clearance and results in lower blood concentrations.

Useful For: Assessing and adjusting quinidine dosage for optimal therapeutic level Assessing quinidine toxicity

Interpretation: Optimal response to quinidine occurs when the serum level is between 2.0 to 5.0 mcg/mL.

Reference Values:
Therapeutic: 2.0-5.0 mcg/mL
Critical value: > or =6.0 mcg/mL


Quinoa (Chenopodium quinoa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L
**Rabbit Epithelium, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rabbit epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
</table>

Reference values apply to all ages.


---

**Rabbit Meat, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rabbit meat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Rabbit Serum Proteins, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to rabbit serum proteins Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
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Reference values apply to all ages.


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**RUPR 82148 Rabbit Urine Proteins, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to rabbit urine proteins Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Rabies Antibody Endpoint

**Interpretation:** Quantitative results. For those who want to know their exact titer between the reportable range. RFFIT stands for Rapid Fluorescent Foci Inhibition Test. It is a serum neutralization (inhibition) test, which means it measures the ability of rabies specific antibodies to neutralize rabies virus and prevent the virus from infecting cells. The antibodies are called rabies virus neutralizing antibodies (RVNA).

**Reference Values:**
- Reportable range is 0.1 to 15.0 IU/mL
- Less than 0.1 IU/mL: Below detection limit

In humans a results of 0.5 IU/mL or higher is considered an acceptable response to rabies vaccination according to the World Health Organization (WHO) guidelines; see WHO and Advisory Committee on Immunization Practices documents for additional guidance.

Radish (Raphanus sativus) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Raji Cell Immune Complex Assay

**Reference Values:**
<= 24 ugE/mL

Many autoimmune disorders, chronic infections and malignancies are associated with circulating immune complexes. Quantitation of immune complexes assists in staging immunologic disorders.

Rape Seed, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to rape seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**RWEED 82616 Rape Weed, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to rape weed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.
Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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MAL 9240

Rapid Malaria/Babesia Smear, Varies

Clinical Information: Malaria is a mosquito-transmitted disease caused by apicomplexan parasites in the genus Plasmodium. It is an important cause of morbidity and mortality worldwide, with the World Health Organization (WHO) estimating 219 million cases and 435,000 malaria-related deaths in 2017. Malaria disproportionately affects individuals living in Africa (90% of cases), with individuals living in southeast Asia and the eastern Mediterranean regions next most affected. Malaria is also encountered outside of endemic regions such as the United States, usually in returning travelers. Malaria is caused primarily by 4 species of the protozoa Plasmodium: P falciparum, P vivax, P malariae, and P ovale. A fifth Plasmodium species, P knowlesi, is a simian parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Babesiosis is an emergent zoonosis caused by an intraerythrocytic protozoan in the genus Babesia. Babesia microti is responsible for the vast majority of human cases in the United States, with "hot spots" of disease along the Northeast Coast (eg, Martha's Vineyard, Long Island, and Nantucket) and Midwest states, although the distribution of disease is spreading. In addition, a small number of cases of Babesia duncani and Babesia duncani-like human infection (WA and CA strains) have been reported along Pacific Coast states from Washington to northern California, and Babesia divergens/B divergens-like strains have been isolated from humans in Missouri (MO-1 strain), Kentucky, and Washington. At this time, only Babesia microti is a nationally notifiable disease. Babesia microti shares a tick vector with Borrelia burgdorferi and Anaplasma phagocytophilum, the causative agents of Lyme disease and human granulocytic anaplasmosis (HGA), respectively. Recent studies suggest that exposure to Babesia microti is quite common in areas endemic for Lyme disease and anaplasmosis, so it is prudent to consider testing for all 3 diseases concurrently. Less commonly, babesiosis may be acquired through blood transfusion, and therefore the FDA approved testing for this parasite in donor units in 2018. Most patients with babesiosis have a mild illness or are asymptomatic, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and
differentiation of Plasmodium and Babesia species. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. This test can also detect trypanosomes that cause Chagas disease (Trypanosoma cruzi) and African sleeping sickness (T. brucei), as well as some species of filariae. If filarial infection is suspected, FIL / Filaria, Blood is recommended since it is more sensitive than the traditional blood smear examination. Examination of the thin film allows for calculation of malaria percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis. The percentage parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Malarial gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalaria drugs.

**Useful For:** Rapid and accurate detection and species identification of Plasmodium Detection of Babesia, trypanosomes, and some species of microfilariae

**Interpretation:** A positive smear indicates infection with the identified species of Plasmodium or with Babesia. Species identification can indicate the appropriate antimalarial therapy.

**Reference Values:**
Negative
  If positive, organism identified and percent parasitemia calculated, if applicable.


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RPRRT 603262

**Rapid Plasma Reagin Screen Response to Therapy, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T. pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Patients with primary or secondary syphilis should be reexamined clinically and serologically 6 months and 12 months following treatment. Typically, rapid plasma reagin (RPR) titers decrease following successful treatment, but this may occur over a period of months to years. Treatment response is generally indicated by a 4-fold (2-tube dilution) reduction in RPR titer (eg, from 1:32 to 1:8). For proper interpretation of RPR results, titers should be obtained using the same testing method, preferably at the same testing laboratory. Failure of nontreponemal test titers to decline 4-fold within 6 months after therapy for primary or secondary syphilis may be indicative of treatment failure. Patients whose titers remain serofast should be reevaluated for HIV infection.

**Useful For:** Determining the current disease status and evaluating response to therapy for syphilis. This test should not be used as a primary diagnostic approach for syphilis. This test is not useful for testing spinal fluid specimens. This test is not intended for medical-legal use.

**Interpretation:** Reactive: Specimen reflexed to determine rapid plasma reagin (RPR) titer value. Nonreactive

**Reference Values:**
Nonreactive

**Clinical References:**

---

RPRS 603261

**Rapid Plasma Reagin Screen with Reflex, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema
pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial non-treponemal screening test, such as the rapid plasma reagin (RPR) or VDRL tests. Because these tests measure the host's antibody response to non-treponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm as described above, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay, such as an enzyme immunoassay (EIA) and multiplex flow immunoassay (MFI), to detect antibodies specific to T pallidum. If the screening assay is positive, the sample is reflexed to a RPR assay, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for T pallidum specific IgG/IgM antibodies using an automated MFI. A positive treponemal test suggests infection with T pallidum, but does not distinguish between recent or past, or treated and untreated infection. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a non-treponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy. In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG/IgM positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, -TP-PA). In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios. In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG/IgM screen. Table 1. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis Total Ab by MFI RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early/acute/primary syphilis) Unknown history of syphilis Reactive Reactive NA Untreated or recently treated syphilis See CDC treatment guidelines Unknown history of syphilis Reactive Nonreactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically indicated (eg, acute/primary syphilis) Unknown history of syphilis Reactive Reactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA NA Reactive or NA Past, successfully treated syphilis None MFI, multiplex flow immunoassay; NA, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination

**Useful For:** Aids in the diagnosis of recent or past Treponema pallidum infection Rapid plasma reagin screening when T pallidum antibody screen is positive This test is not useful as a screening or confirmatory test for blood donor specimens.

**Interpretation:** Nonreactive: Treponema pallidum particle agglutination (TP-PA) has been ordered to distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result Reactive: Specimen reflexed to determine rapid plasma reagin (RPR) titer value

**Reference Values:**
Only available as a reflex test. For more information see SYPHT / Syphilis Total Antibody with Reflex, Serum.

Nonreactive

RAS/RAF Targeted Gene Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with solid tumors. These data can also be used to help determine clinical trial eligibility for patients with mutations in genes not amenable to current FDA-approved targeted therapies. The epidermal growth factor receptor (EGFR) gene product is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with colorectal cancer. Assessment for BRAF mutations has clinical utility in that it is a predictor of response to antimitant BRAF therapy. BRAF is a member of the mitogen-activated protein/ extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success with increases both in progression-free and overall survival in patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components. See Targeted Gene Regions Interrogated by RAS/RAF Gene Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

Useful For: Identifying tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously Identifying mutations that may help determine prognosis for patients with solid tumors Identifying specific mutations within genes known to be associated with response or resistance to specific cancer therapies

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

FRASP 57665  Raspberry IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

RASP 86305  Raspberry, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to raspberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**RAT 82725**

**Rat Epithelium, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
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<tr>
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<td>2</td>
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<td>3</td>
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<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**RTSP 82793**

**Rat Serum Protein, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rat serum protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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<td>Strongly positive</td>
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Reference values apply to all ages.


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**Rat Urine Protein, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rat urine protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**RAVUM 609500**

**Ravulizumab Complement Blockage Monitoring, Serum**

**Clinical Information:** Ravulizumab (Ultomiris, Alexion Pharmaceuticals) is a humanized hybrid monoclonal antibody (IgG2/IgG4) that blocks complement C5 cleavage, thereby preventing the activation of the proinflammatory effects of C5a and the cytolysic effects of the membrane attack complex (MAC) formed by C5b-C9. It is FDA-approved for atypical hemolytic uremic syndrome,(1) and paroxysmal nocturnal hemoglobinuria.(2) Compared to its predecessor eculizumab, ravulizumab is a longer-acting therapeutic monoclonal antibody. There are 4 amino acid changes in ravulizumabâ€™s heavy chain in comparison to eculizumab. These changes resulted in more affinity for the FcRn receptor which recycles immunoglobulins instead of degrading them, and changes in the variable region of the heavy chain made it possible for C5 to be released from ravulizumab molecule, so that C5 is left alone inside the endosome to be degraded. The dosing regimen for ravulizumab is weight-based, and after a loading dose schedule, the maintenance therapy requires administration intravenously every 8 weeks. Therapy efficacy may be monitored by measuring efficiency of complement blockade. Ravulizumab will affect complement function assays that rely on the formation of the MAC to generate cell lysis. Validation studies performed by the Mayo Clinic show that the alternative pathway (AH50) enzyme-linked immunosorbent assayÂ is the most helpful of the complement tests to monitor efficacy of the complement blockage by ravulizumab. Ravulizumab serum concentrations greater than 200 mcg/mL inhibited the AH50 activity completely, and 0% activity was detected at all subsequent tested concentrations up to 1000 mcg/mL.

**Useful For:** Monitoring of complement blockage by ravulizumab Investigation of suspected alternative pathway complement deficiency, atypical hemolytic uremic syndrome, C3 glomerulonephritis, dense-deposit disease

**Interpretation:** In clinical trials for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (HUS), therapeutic concentrations of ravulizumab were established as greater than 175 mcg/mL. For the complement blockage monitoring of ravulizumab: -When ravulizumab is present in serum at concentrations around 50 mcg/mL, the results range from 20% to 29% of normal.
-When ravulizumab concentrations are around 100 mcg/mL, the results range from 8% to 13% of normal.
-When ravulizumab concentrations are greater than 200 mcg/mL, the results are below the limit of quantitation of the assay (<10% of normal).
Reference Values:
> or =46% normal

Clinical References:

Ravulizumab, Serum

RAVU 609420

Clinical Information: Ravulizumab (Ultomiris, Alexion Pharmaceuticals) is a humanized monoclonal IgG2/4 kappa antibody therapeutic directed against the complement component 5 (C5). By association with C5, ravulizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Since all 3 arms of the complement cascade converge at the point of C5 activation, targeted by ravulizumab, this drug may have broad potential application and is being clinically evaluated in other disorders with complement over-activation. Since ravulizumab demonstrated noninferiority to eculizumab in clinical trials for both paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), there is likelihood of patients being moved from eculizumab to ravulizumab therapy. Ravulizumab is a longer-acting hybrid IgG2/IgG4 therapeutic monoclonal antibody (145 kDa). Its sequence is very similar to eculizumab (148 kDa), except for a 4 amino acid difference in the heavy chain of the molecule. Eculizumab binds to complement component C5 in the intravascular space and, after the resulting eculizumab-C5 complex is taken up by endothelial cells, it is degraded in the endosomes. In order to increase its half-life, two changes were made to ravulizumab: 2 amino acids substituted in the constant region give ravulizumab more affinity for the Brambell receptor (FcRn), which recycles IgG instead of degrading it. The other 2 amino acids changes are in the variable region of the heavy chain, changing the affinity of the Fab fraction for C5, making it possible for C5 to be released from ravulizumab before it is recycled, so that C5 is left alone inside the endosome to be degraded. Eculizumab is administered as a standard (non-weight based) dose for approved conditions. Ravulizumab's key improvements over eculizumab include the longer half-life, leading to IV infusions every 8 weeks instead of every 2 weeks, along with a weight-based dosing schedule that further personalized therapy regimens. Some patients who persist with serum concentrations above therapeutic targets with complete complement blockade could benefit from dose de-escalation or prolonged infusion intervals, and visit the clinic for infusions less frequently than the FDA-label 2 weeks. Therapeutic drug monitoring of ravulizumab could result in cost-savings and improved quality of life if target therapeutic concentrations can be achieved with complete complement system blockade at less frequent dosing intervals.

Useful For: Assessing the response to ravulizumab therapy Assessing the need for dose escalation Evaluating the potential for dose de-escalation or discontinuation of therapy in remission states Monitoring patients who need to be above a certain ravulizumab concentration in order to improve the odds of a clinical response for therapy optimization This test is not useful as the sole basis for a diagnosis or treatment decisions.
**Interpretation:** Target trough therapeutic concentrations (immediately before next infusion) of ravulizumab are expected to be above 175 mcg/mL for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Pharmacodynamic studies of complement blockage may also be recommended for patients undergoing therapy.

**Reference Values:**
Lower limit of quantitation=5.0 mcg/mL

>175 mcg/mL-Therapeutic concentration for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome

**Clinical References:**

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**Recombx MaTa Autoantibody Test**

**Reference Values:**
A final report will be attached in MayoAccess.

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**Recoverin-IgG Antibody, Immunoblot, Serum**

**Clinical Information:** Patients with recoverin autoimmunity present with insidious onset vision change, often night-vision loss, floaters, and constricted vision, that can rapidly progress to blindness. On ophthalmologic examination, there are features of non-inflammatory retinopathy; retinal and optic nerve head pallor/atrophy, constricted visual fields and flat electroretinogram (ERG), but without anterior chamber disease, which is encountered with CRMP-5 paraneoplastic ophthalmitis. Small cell (pulmonary or extrapulmonary) or neuroendocrine carcinoma should be sought. Trials of immunotherapy could be attempted to improve vision, though generally this is not successful.

**Useful For:** Evaluating patients with suspected paraneoplastic retinopathy accompanying small cell carcinoma

**Interpretation:** Seropositivity is consistent with a diagnosis of paraneoplastic retinopathy. Small cell carcinoma (pulmonary or extrapulmonary) and neuroendocrine carcinoma should be considered.

**Reference Values:**
Negative

**Clinical References:**
Red Blood Cell (RBC) Enzyme Evaluation, Blood

Clinical Information: Erythrocyte enzyme deficiencies are inherited causes of hemolytic anemia. Some are very common, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, and others are very rare, found in only a few families around the world. Most are autosomal in inheritance, but some are sex-linked and located on the X chromosome. Most enzyme deficiencies result in chronic nonspherocytic hemolytic anemia of variable severity; however, some, such as G6PD, can be hematologically normal with episodic acute hemolysis due to a trigger event such as medications, toxins, or some foods. The RBC enzymopathies do not typically show recurrent pathognomonic changes on the peripheral blood smear other than generic features of hemolytic anemia, although some such as pyruvate kinase deficiency can have echinocytes and pyrimidine 5’ nucleotidase (P5NT) deficiency is associated with basophilic stippling. RBC enzyme activity levels are best evaluated as a panel as reticulocytosis can mask some deficient states and comparison to the background enzyme activity is useful. This is a consultative evaluation of red cell enzyme activity as a potential cause of early red cell destruction.

Useful For: Identifying defects of red cell enzyme metabolism Evaluating patients with Coombs-negative hemolytic anemia

Interpretation: A hematopathologist expert in these disorders evaluates the case and an interpretive report is issued.

Reference Values: Definitive results and an interpretive report will be provided.


Red Blood Cell (RBC) Enzyme Interpretation

Clinical Information: Erythrocyte enzyme deficiencies are inherited causes of hemolytic anemia. Some are very common, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, and others are very rare, found in only a few families around the world. Most are autosomal in inheritance, but some are sex-linked and located on the X chromosome. Most enzyme deficiencies result in chronic nonspherocytic hemolytic anemia of variable severity; however, some, such as G6PD, can be hematologically normal with episodic acute hemolysis due to a trigger event such as medications, toxins, or some foods. The RBC enzymopathies do not typically show recurrent pathognomonic changes on the peripheral blood smear other than generic features of hemolytic anemia, although some such as pyruvate kinase deficiency can have echinocytes and pyrimidine 5’ nucleotidase (P5NT) deficiency is associated with basophilic stippling. RBC enzyme activity levels are best evaluated as a panel as reticulocytosis can mask some deficient states and comparison to the background enzyme activity is useful. This is a consultative evaluation of red cell enzyme activity as a potential cause of early red cell destruction.

Useful For: Interpretation of results for the red blood cell enzyme evaluation Identifying defects of red cell enzyme metabolism Evaluating patients with Coombs-negative hemolytic anemia

Interpretation: A hematopathologist expert in these disorders evaluates the case and an interpretive report is issued.

Reference Values: Only orderable as part of a profile. For more information see EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood.

Definitive results and an interpretive report will be provided.
Red Blood Cell Enzyme Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This panel aids in the diagnosis and genetic counseling of individuals with inherited RBC enzymopathies, possible carrier states, or compound mutations with severity modulating interactions. This panel always should be interpreted in the context of protein functional findings by enzymatic assay and complete blood count and peripheral blood findings. This complete interpretation can be provided by also ordering the EEEVP / RBC Enzyme Evaluation. Please fill out the information sheet and indicate that NGS testing was ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results. Mature erythrocytes are dependent upon glycolysis for energy production and the hexose monophosphate shunt for oxidation-reduction stability. Hereditary deficiencies in RBC enzymes within these pathways cause nonspherocytic hemolytic anemia (NSHA) with variable clinical presentations, therapeutic considerations and inheritance patterns.(1-3) Most of these deficiencies cause chronic hemolysis with little to no pathognomonic morphologic changes in the peripheral blood smear making correlation with enzyme activity critical for diagnosis. Some are associated with acute episodic anemia triggered by medications, food, or viral illness. Variable additional symptoms may be present for some deficiency types, including myopathy, neuropathy, and developmental delay. Because a subset of clinically significant RBC enzyme disorders can have indeterminate to normal enzyme activity (masking in the presence of increased reticulocytes), the protein enzymatic activity studies are more sensitive when performed as a panel of RBC enzymes, which allows comparison of multiple enzyme activities. This genetic panel can aid in the interpretation of equivocal protein findings and genetically confirm an enzyme deficiency. Additionally, there are genes interrogated on this panel for which an enzyme test is not clinically available for correlation.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an underlying RBC enzymopathy Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(4,5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

Red Blood Cell Membrane Evaluation, Blood

Clinical Information: The functional red cell membrane is composed of a cholesterol and phospholipid bilayer anchored by integral proteins to an elastic cytoskeletal network. These interactions form the shape, deformability, and proper ion balance of the cell. Abnormalities in these moieties result in red blood cell membrane disorders. Hereditary spherocytosis (HS) is a common membrane disorder that can be present in many ethnic groups. Its prevalence has been estimated at approximately 1 in 3,000 persons of Northern European ancestry. It is usually associated with visible spherocytes on the peripheral blood smear and can be associated with variable clinical features of hemolysis ranging from completely compensated to mild to severe. Hereditary elliptocytosis (HE) is another fairly common and clinically variable disorder that can range from normal RBC indices in the large majority of cases to rare patients with moderate to severe anemia. Common hereditary elliptocytosis (CHE) is characterized by the presence of elliptocytes on the peripheral blood smear. Mutations associated with HE have been reported in widely variable ethnicities with greater prevalence in populations overlapping the malaria belt. Hereditary pyropoikilocytosis (HPP) is best classified as a severe form of hereditary elliptocytosis. It is uncommon and presents in early childhood as a severe hemolytic anemia. These disorders are associated with marked poikilocytosis on the peripheral blood smear. (1,2) Red cell membrane disorders can result from abnormalities involving several red cell membrane proteins, such as band 3, alpha and beta spectrin, protein 4.1, protein 4.2, glycoporphin C, and ankyrin. Most often, red cell membrane disorders are diagnosed in childhood, adolescence, or early adult life. The diagnosis of HS is usually made by a combination of patient and family history, laboratory evidence of hemolysis, and review of a peripheral blood smear. The osmotic fragility (OF) test is usually markedly abnormal in HS cases. However, factors such as age, iron status, and medications can affect the OF test. The OF test is nonspecific and can be increased in acquired disorders such as autoimmune hemolytic anemia. Coombs testing should be negative prior to ordering this test. The addition of eosin-5-maleimide (EMA) binding (Band3) flow cytometry to this profile increases specificity if a typical moderately decreased pattern is present. Hereditary pyropoikilocytosis can have normal or only mildly increased OF results and often displays a very dim and sometimes dual peak pattern with EMA-binding testing. Common hereditary elliptocytosis cases are not discriminated from normal patients in either OF and EMA binding (band3) testing and this profile does not add confirmatory information for HE.

Useful For: Investigation of suspected red cell membrane disorders such as hereditary spherocytosis or hereditary pyropoikilocytosis

Interpretation: An interpretive report will be provided.

Reference Values:

> or =12 months:

- 0.50 g/dL NaCl (unincubated): 3-53% hemolysis
- 0.60 g/dL NaCl (incubated): 14-74% hemolysis
- 0.65 g/dL NaCl (incubated): 4-40% hemolysis
- 0.75 g/dL NaCl (incubated): 1-11% hemolysis

An interpretive report will be provided.

Reference values have not been established for patients who are <12 months of age.

NGMEM
64938

**Red Blood Cell Membrane Panel, Next-Generation Sequencing, Varies**

**Clinical Information:** Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This test is best interpreted in the context of protein studies and peripheral blood findings. This can be provided by also ordering the RBCME / Red Blood Cell Membrane Evaluation test. Please fill out the information sheet and indicate that NGS testing was ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results. This panel aids in the diagnosis and genetic counseling of individuals with RBC membrane disorders including hereditary spherocytosis, hereditary elliphtocytosis, hereditary pyropoikilocytosis, Southeast Asian ovalocytosis, hereditary stomatocytosis (both overhydrated and dehydrated/hereditary xerocytosis subtypes), and cryohydrocytosis(1-3). The functional red cell membrane is composed of a cholesterol and phospholipid bilayer anchored by integral proteins to an elastic cytoskeletal network. These interactions form the shape, deformability, and proper ion balance of the cell. Abnormalities in these moieties result in red blood cell membrane disorders. Hereditary spherocytosis (HS) is a common membrane disorder that can be present in all ethnic groups. It is usually associated with visible spherocytes on the peripheral blood smear and can be associated with variable clinical features of hemolysis ranging from mild to severe. Paradoxically, erythrocytosis can occur after splenectomy. Hereditary elliphtocytosis (HE) is another fairly common and clinically variable disorder that can range from normal RBC indices in the large majority of cases to a minor subset of patients with moderate to severe anemia. Common hereditary elliphtocytosis (CHE) is characterized by the presence of elliphtocytes on the peripheral blood smear and the absence of anemia. Mutations associated with HE have been reported in widely variable ethnicities with greater prevalence in populations overlapping the malaria belt. Hereditary pyropoikilocytosis (HPP) is now best classified as a severe form of hereditary elliphtocytosis. It is uncommon and presents in early childhood as a severe hemolytic anemia. These disorders are associated with marked poikilocytes on the peripheral blood smear.(1,2) Hereditary stomatocytosis is an RBC membrane permeability disorder that can manifest as the more common dehydrated hereditary stomatocytosis (DHSt), also known as hereditary xerocytosis (HX), and the rarer overhydrated hereditary stomatocytosis (OHSt) subtypes. These disorders are important to confirm or exclude as splenectomy has been associated with an increased risk for serious venous thrombosis and thromboembolism events and is contraindicated in published guidelines.(4) DHSt/HX manifests variably as mild to compensated anemia to some cases with increased hemoglobin levels. Some patients are asymptomatic, others show hemolysis after even nontraumatic exercise sessions. Others display perinatal edema and susceptibility to iron overload. DHSt/HX is associated with pseudohyperkalemia, increased MCHC, and decreased osmotic fragility due to relative dehydration of the red blood cell. OHSt is similarly is associated with anemia of variably severity, but is associated with increased osmotic fragility due to a relatively overhydrated steady state.

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an RBC membrane disorder Second-tier testing for patients in whom previous targeted gene mutation analyses were negative for a specific RBC membrane disorder Establishing a diagnosis of a hereditary RBC membrane disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration (4) Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(5,6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.
Reference Values:
An interpretive report will be provided.


Red Currant, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to red currant Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Red Snapper (Lutjanus spp) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 Â– 0.34
Equivocal/Borderline 1 0.35 Â– 0.69 Low Positive 2 0.70 Â– 3.49 Moderate Positive 3 3.50 Â– 17.49 High Positive 4 17.50 Â– 49.99 Very High Positive 5 50.00 Â– 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

Red Sorrel, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to red sorrel
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>3.50-17.4</td>
</tr>
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<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
</tbody>
</table>
| 6             | > or =100            | Strongly positive Reference values apply to all ages.

Red Top, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to red top Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Reducing Substance, Feces

Clinical Information: Fecal reducing substances (carbohydrates) aids in determining the underlying cause of diarrhea. Elevations in fecal reducing substances help distinguish between osmotic diarrhea caused by abnormal excretion of various sugars as opposed to diarrhea caused by viruses and parasites. Increased reducing substances in stool are consistent with, but not diagnostic of, primary or secondary disaccharidase deficiency (primarily lactase deficiency) or intestinal monosaccharide malabsorption. Similar intestinal absorption deficiencies are associated with short bowel syndrome and necrotizing enterocolitis.

Useful For: Assisting in the differentiation between osmotic and non-osmotic diarrhea Screening test for: - Diarrhea from disaccharidase deficiencies, (eg, lactase deficiency) - Monosaccharide malabsorption
**Interpretation:** Negative: negative Normal: < or =0.25 g/dL (trace) Suspicious: >0.25 to 0.50 g/dL (grade 1) Abnormal: >0.50 g/dL (grade 2-4)

**Reference Values:**
Negative or trace

**Clinical References:**

**Relative B-Cell Subset Analysis Percentage, Blood**

**Clinical Information:** The adaptive immune response includes both cell-mediated (mediated by T cells and NK cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are of 3 subsets: marginal zone B cells (MZ or nonswitched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both, result in immune deficiency states and increased susceptibility to infections. These decreases may be either primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1:25,000 to 1:50,000. CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years of age, or occasionally even later. Four different genetic defects have been associated with CVID, including mutations in the ICOS, CD19, BAFF-R, and TACI genes. The first 3 genetic defects account for approximately 1% to 2%, and TACI mutations account for 8% to 15% of CVID cases. CVID is characterized by hypogammaglobulinemia usually involving most or all of the Ig classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections. (1,2) B-cell numbers may be normal or decreased. A minority of CVID patients (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency. (1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4:CD8 ratio (<1). Studies have shown the clinical relevance of classifying CVID patients by assessing B-cell subsets, since changes in different B-cell subsets are associated with particular clinical phenotypes or presentations. (3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA. (5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects—mutations in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes. (5) Mutations in CD40L and NEMO are inherited in an X-linked fashion, while mutations in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increase in nonswitched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depleting therapies, such as Rituxan (Rituximab) and Zevalin (Ibritumomab tiuxetan).

**Useful For:** Screening for humoral or combined immunodeficiencies, including common variable immunodeficiency (CVID), hyper IgM syndrome, among others, where B-cell subset distribution information is desired Assessing B-cell subset reconstitution after hematopoietic cell (HCT) or bone marrow transplant Assisting B-cell subset reconstitution following recovery of B cells after
B-cell-depleting immunotherapy

**Interpretation:** The assay provides semiquantitative (%) information on the various B-cell subsets. Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: -CD19+=B cells expressing CD19 as a percent of total lymphocytes -CD19+ CD27+=total memory B cells -CD19+ CD27+ IgD+=marginal zone or non-switched memory B cells -CD19+ CD27- IgD-=class-switched memory B cells -CD19+ IgM+=IgM-only memory B cells -CD19+ CD27+ IgD- IgM- =class-switched memory B cells -CD19+ IgM+=IgM B cells -CD19+ CD38+ IgM+=transitional B cells -CD19+ CD38+ IgM+=plasmablasts -CD19+ CD21-=CD21-negative B cells -CD19+ CD21+=CD21-positive B cells -CD19+ CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes For isotype class-switching and memory B-cell analyses, the data will be reported as being consistent or not consistent with a quantitative defect in memory subsets and/or class switching. If a defect is present in any of these B-cell subpopulations, further correlation with clinical presentation and additional functional, immunological, and genetic laboratory studies will be suggested, if appropriate.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

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**Renal Cell Carcinoma, 6p21.1 (TFEB) Rearrangement, FISH, Tissue**

**Clinical Information:** The TFEB gene may be altered in some patients with renal cell carcinoma (RCC). Identification of rearrangement of the TFEB gene region by FISH analysis can aid in the diagnosis of RCC.

**Useful For:** Identifying TFEB gene rearrangements in patients with renal cell carcinoma (RCC)

**Interpretation:** A positive result with the TFEB probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of TFEB suggests promotor substitution caused by structural alterations of the TFEB gene region at 6p21.1. A negative result suggests no structural alterations of the locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Renal Function Panel, Serum

Clinical Information: A renal function panel could be ordered when a patient has risk factors for kidney dysfunction such as high blood pressure (hypertension), diabetes, cardiovascular disease, obesity, elevated cholesterol, or a family history of kidney disease. A renal function panel may also be ordered when someone has signs and symptoms of kidney disease, though early kidney disease often does not cause any noticeable symptoms. It may be initially detected through routine blood or urine testing.

Useful For: Aids in diagnosis and management of conditions affecting kidney function General health screening Screening patients at risk of developing kidney disease Management of patients with known kidney disease

Interpretation: Renal function panel results are not diagnostic but rather indicate that there may be a problem with the kidneys and that further testing is required to make a diagnosis and determine the cause. Results of the panel are usually considered together, rather than separately. Individual test result can be abnormal due to causes other than kidney disease, but taken together with risks and signs and symptoms, they may give an indication of whether kidney disease is present.

Reference Values:
SODIUM
<1 year: not established
> or =1 year: 135-145 mmol/L

POTASSIUM
<1 year: not established
> or =1 year: 3.6-5.2 mmol/L

CHLORIDE
<1 year: not established
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L

BICARBONATE
Males
<1 year: not established
1-2 years: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L
Females
<1 year: not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: not established
> or =7 years: 7-15

BLOOD UREA NITROGEN (BUN)
Males
<12 months: not established
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL
Females

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

Page 2194
<12 months: not established
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL

CREATININE
Males
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL
Females
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

eGFR
>60 mL/min/BSA
Estimated GFR calculated using the 2009 CKD_EPI creatinine equation.

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: not established
> or =1 year: 70-140 mg/dL
Total Protein
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are <12 months of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are <12 months of age.

PHOSPHORUS
Males
1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are less than 12 months of age.
Females
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are less than 12 months of age.

Renal Pathology Consultation, Wet Tissue

Clinical Information: The Mayo Renal Pathology service is staffed by board-certified pathologists who have a special interest in non-neoplastic diseases of the kidney. Kidney biopsy has proven to be of value in the clinical evaluation and management of patients with kidney disease, including acute and chronic renal insufficiency, nephrotic syndrome, nephritic syndrome, proteinuria and hematuria, and in the overall management of renal transplant recipients. Optimal interpretation of a kidney biopsy requires integration of clinical and laboratory results with light microscopic, immunofluorescent histology, and electron microscopy findings.

Useful For: Evaluating and managing patients with kidney disease Following the progression of known renal disease or response to therapy Determining the cause of dysfunction in the transplanted kidney (allograft)

Interpretation: Both a verbal report and a faxed report are provided to nephrologists for Mayo Clinic Laboratories cases. Representative electron microscopy images and significant positive immunofluorescent stain findings can be provided on a CD upon request. In most cases, the electron microscopy results are reported as an addendum and a final report is issued including these findings. This final report is again faxed to the submitting nephrologist and mailed to the submitting pathology laboratory, along with a representative set of the light microscopy slides.

Reference Values: An interpretive report will be provided.


Renin Activity, Plasma

Clinical Information: The renal juxtaglomerular apparatus generates renin, an enzyme that converts angiotensinogen to angiotensin I. The inactive angiotensin I is enzymatically converted to the active octapeptide angiotensin II, a potent vasopressor responsible for hypertension of renal origin. Angiotensin II also stimulates the zona glomerulosa of the adrenal cortex to release aldosterone. Renin secretion by the kidney is stimulated by a fall in glomerular blood pressure, by decreased sodium concentration at the macula densa at the distal tubule, or by stimulation of sympathetic outflow to the kidney, such as in renal vascular diseases.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) Not useful for determination of plasma renin concentration.

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. A SA:PRA ratio > or =20 and SA of > or =15 ng/dL indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected:normal) above 1.5. See Renin-Aldosterone Studies in Special Instructions.

Reference Values:

- 0-2 years: 4.6 ng/mL/hour (mean)* Range: 1.4-7.8 ng/mL/hour
- 3-5 years: 2.5 ng/mL/hour (mean)* Range: 1.5-3.5 ng/mL/hour
- 6-8 years: 1.4 ng/mL/hour (mean)* Range: 0.8-2.0 ng/mL/hour
- 9-11 years: 1.9 ng/mL/hour (mean)* Range: 0.9-2.9 ng/mL/hour
12-17 years: 1.8 ng/mL/hour (mean)* Range: 1.2-2.4 ng/mL/hour
Mean data not standardized as to time of day or diet. Infants were supine, children sitting.

Na-depleted, upright (peripheral vein specimen)
18-39 years: 10.8 ng/mL/hour (mean)
2.9-24.0 ng/mL/hour (range)
≥40 years: 5.9 ng/mL/hour (mean)
2.9-10.8 ng/mL/hour (range)

Na-replete, upright (peripheral vein specimen)
18-39 years: 1.9 ng/mL/hour (mean)
<0.6-4.3 ng/mL/hour (range)
≥40 years: 1.0 ng/mL/hour (mean)
<0.6-3.0 ng/mL/hour (range)


Clinical References:

RTSC
602185

Reptilase Time, Plasma

Clinical Information: Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of any of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time (PT) and activated partial thromboplastin time (APTT) are first-order tests for coagulation abnormalities and are prolonged in many bleeding disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. The thrombin time (TT) test is used to identify the cause of prolonged APTT or dilute Russell viper venom time (DRVVT). Reptilase time (RT) test is used to evaluate a prolonged TT. Reptilase is a thrombin-like enzyme isolated from the venom of Bothrops atrox. Thrombin splits small fibrinopeptides A and B from fibrinogen molecules, producing fibrin monomer, which polymerizes to form a clot. Reptilase, however, splits off fibrinopeptide A but not B, which results in fibrin polymerization. In contrast to thrombin and the TT test which are inhibited by heparin, the RT is normal in the presence of heparin. Similar to the TT test, the RT is prolonged in the presence of hypofibrinogenemia and dysfibrinogenemia.

Useful For: Evaluation of a prolonged thrombin time (TT): It is mainly used to confirm or exclude the presence of heparin in the specimen or specimen type Evaluating hypofibrinogenemia or dysfibrinogenemia in conjunction with the TT and fibrinogen assay

Interpretation: As seen in the following table, reptilase time can help distinguish among the various causes of a prolonged thrombin time (TT). Thrombin Time Reptilase Time Causes Remarks Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay

Reference Values:
14.0-23.9 seconds

Clinical References:
Respiratory Panel, PCR, Nasopharyngeal

**Clinical Information:** Respiratory infections are common and generally cause self-limited illnesses in healthy, immunocompetent hosts. Viruses account for a significant percentage of respiratory diseases, but bacteria can be associated with respiratory infections. Although respiratory illnesses are frequently mild, viruses may cause significant morbidity and mortality in immunocompromised hosts (e.g., transplant recipients, patients with underlying malignancies). Influenza viruses (types A and B) and respiratory syncytial virus (RSV) are 2 common causes of viral respiratory illness, with peak incidence in the winter and spring months in the Northern hemisphere. Both viruses can cause a clinically indistinguishable syndrome, characterized by fever, cough, headache, and general malaise. RSV is a leading cause of respiratory illness in young children. Early diagnosis of influenza and RSV is important so that 1) necessary infection control precautions can be taken if the patient is hospitalized, and 2) antiviral therapy can be considered if the patient is hospitalized or considered at high-risk for severe disease. Human metapneumovirus is also a cause of respiratory illness in both children and adults. Human rhinovirus and coronavirus serotypes HKU1, NL63, 229E, OC43 are the causative agents of the common cold, with symptoms including runny nose, sore throat, and malaise. Infections with rhinovirus and coronaviruses are extremely common, due to the large number of serotypes of these viruses. Most infections are mild and self-limiting; however, immunocompromised hosts may suffer more severe illnesses, including lower respiratory tract disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (e.g., the common cold) to severe (e.g., pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms may be nonspecific and resemble other common respiratory infections, such as influenza. Parainfluenza viruses and adenovirus are also common causes of viral infection, especially in young children. Parainfluenza viruses are most common during the spring, summer, and fall months, with symptoms including fever, runny nose, and cough. However, parainfluenza viruses may also cause more severe lower respiratory disease, such as croup or pneumonia. Adenoviruses may infect a range of organ systems, with sequelae ranging from cold-like symptoms (sore throat) to pneumonia, conjunctivitis (pink eye), or diarrhea. Similarly to the viruses described above, parainfluenza viruses and adenoviruses generally cause mild, self-limited infections but may cause severe disease in immunosuppressed patients. Respiratory infections may also be caused by bacterial pathogens, including Bordetella pertussis, Bordetella parapertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae. B pertussis is the causative agent of pertussis, or whooping cough, a disease characterized by prolonged cough that may be associated with an inspiratory whoop and post-tussive vomiting. B parapertussis causes a similar, but generally less severe, illness. M pneumoniae is a cause of upper respiratory infection, pharyngitis, tracheobronchitis, and pneumonia. C pneumoniae is a rare cause of pneumonia.

**Useful For:** Rapid detection of respiratory infections caused by the following: - Adenovirus - Coronavirus (serotypes HKU1, NL63, 229E, OC43) - Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - Human metapneumovirus - Human rhinovirus/enterovirus - Influenza A (H1, H1-2009, H3) - Influenza B - Parainfluenza virus (serotypes 1-4) - Respiratory syncytial virus (RSV) - Bordetella pertussis - Bordetella parapertussis - Chlamydia pneumoniae - Mycoplasma pneumoniae - Mycoplasma pneumoniae This test is not recommended as a test of cure.

**Interpretation:** Results are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. A negative result should not rule out infection in patients with a high pretest probability for a respiratory infection. The assay does not test for all potential infectious agents of respiratory disease. Specimens collected too early or too late in the clinical course may not yield the organism causing disease. Negative results should be considered in the context of a patient's clinical course and treatment history, if applicable. For patients who are immunocompromised and have a negative FilmArray respiratory panel test from a nasopharyngeal sample but a high suspicion for infection, there may be additional value in testing a bronchoalveolar lavage specimen (RESLR / Respiratory Pathogen Panel, PCR, Varies). Positive results do not distinguish between a viable or replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not included in the panel. Nucleic acid may persist...
in some patients for days to weeks, even following appropriate therapy. Detection of 1 or more organisms included in this test suggests that the virus or bacteria is present in the clinical sample; however, the test does not distinguish between organisms that are causing disease and those that are present but not associated with a clinical illness. Coinfections (eg, detection of multiple viruses or bacteria or viruses and bacteria) may be observed with this test. In these situations, the clinical history and presentation should be reviewed thoroughly to determine the clinical significance of multiple pathogens in the same specimen.

Reference Values:
Undetected (for all targets)


Respiratory Pathogen Panel, PCR, Varies

Clinical Information: Respiratory infections are common and generally self-limited in healthy, immunocompetent hosts. Viruses account for a significant percentage of respiratory diseases, but bacteria are also associated with respiratory infections, including pneumonia. Although respiratory illnesses are frequently mild, viruses and bacteria may cause significant morbidity and mortality in immunocompromised hosts (eg, transplant recipients, patients with underlying malignancy); however, there is potential for prolonged shedding of microorganisms or nucleic acids in immunocompromised patients without their necessarily causing clinical disease; laboratory results should be interpreted in the context of clinical findings. Influenza viruses (type A and type B) and respiratory syncytial virus (RSV) are 2 common causes of viral respiratory illness, with peak incidence in the winter and spring months in the Northern hemisphere. Both viruses can cause a clinically indistinguishable syndrome, characterized by fever, cough, headache, and general malaise. RSV is a leading cause of respiratory illness in young children. Early diagnosis of influenza and RSV is important so that 1) necessary infection control precautions can be taken if the patient is hospitalized, and 2) antiviral therapy can be considered if the patient is hospitalized or considered at high-risk for severe disease.(1) Human metapneumovirus is a relative of RSV, and is also a cause of respiratory illness in both children and adults. Human rhinovirus and coronavirus (serotypes HKU1, NL63, 229E, OC43) are the causative agents of the common cold, with symptoms including runny nose, sore throat, and malaise. Infections with rhinovirus and coronaviruses are common due to the large number of serotypes of these viruses. The vast majority of infections are mild and self-limiting; however, immunocompromised hosts may suffer more severe illness, including lower respiratory tract disease. Parainfluenza viruses are a common cause of mild, self-limiting viral infections, especially in young children. Infections are most common in the spring, summer, and fall months, with symptoms including fever, runny nose, and cough; however, parainfluenza may also cause more severe lower respiratory disease, such as croup or pneumonia particularly in older adults or immunocompromised patients. Adenoviruses may infect a range of organ systems, with sequelae ranging from cold-like symptoms (sore throat), to pneumonia, conjunctivitis (pink eye), or diarrhea. Adenoviruses generally cause mild, self-limited infections but may cause severe disease in immunosuppressed patients. Respiratory infections may also be caused by bacterial pathogens, including Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma (Mycoplasma) pneumoniae. Bordetella pertussis is the causative agent of pertussis, or whooping cough, a disease characterized by persistent cough that may be associated with an inspiratory whoop and post-tussive vomiting. Mycoplasma pneumoniae is a cause of upper respiratory infection, pharyngitis, tracheobronchitis, and pneumonia. Chlamydia pneumoniae is a rare cause of pneumonia.

Useful For: Rapid detection of respiratory infections caused by the following: -Adenovirus -Coronavirus (serotypes HKU1, NL63, 229E, OC43) -Human metapneumovirus -Human rhinovirus/enterovirus -Influenza A (H1, H1-2009, H3) -Influenza B -Parainfluenza virus (serotypes...
**Interpretation:** Results of the panel are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. A negative result should not rule-out infection in patients with a high pretest probability for a respiratory infection. The assay does not test for all potential infectious agents of respiratory disease. Samples collected too early or too late in the clinical course may not yield the organism causing disease. Negative results should be considered in the context of a patient's clinical course and treatment history, if applicable. Positive results do not distinguish between a viable/replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not contained within the panel. Nucleic acid may persist in some patients for days to weeks, even following appropriate therapy. Detection of 1 or more organisms included in this test suggests that the virus/bacterium is present in the clinical sample; however, the test does not distinguish between organisms that are causing disease and those that are present but not associated with a clinical illness. Coinfections (eg, detection of multiple viruses or bacteria or viruses and bacteria) may be observed with this test. In these situations, the clinical history and presentation should be reviewed thoroughly to determine the clinical significance of multiple pathogens in the same specimen.

**Reference Values:**
Negative (for all targets)

**Clinical References:**

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**Respiratory Profile, Region 1, North Atlantic (CT, MA, ME, NJ, NH, NY, PA, RI, VT), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually
manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the North Atlantic region including Connecticut, Maryland, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<th>Interpretation</th>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>5</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages.

**Total IgE:**

Results Reported in kU/L

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<tr>
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</tr>
<tr>
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**Clinical References:**
**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Southwestern Grasslands region including Oklahoma and Texas Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages. Total IgE:

Results Reported in kU/L

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RPR11
62057

Respiratory Profile, Region 11, Rocky Mountain (AZ [Mt]; CO; ID [Mt]; NM, UT [Mt]; WY), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Rocky Mountain region including Arizona, Colorado, Idaho, New Mexico, Utah and Wyoming Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an
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**Respiratory Profile, Region 12, Arid Southwest (Southern AZ Desert, Southern CA Desert), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and...
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Useful For: Assessing sensitization to various inhalant allergens commonly found in the Arid Southwest region including the southern Arizona desert and the southern California desert Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tr>
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Reference values apply to all ages. Total IgE:

Results Reported in kU/L

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<td>18 years and older</td>
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**Respiratory Profile, Region 13, Southern Coastal California, Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Southern Coastal California region Defining the allergen responsible for eliciting signs and symptoms Identifying allergens - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>


Respiratory Profile, Region 14, Central California, Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Central
Defining the allergen responsible for eliciting signs and symptoms

- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages. Total IgE:</td>
</tr>
</tbody>
</table>

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months</td>
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<td>&lt; or =537</td>
</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>

**Clinical References:**


**Respiratory Profile, Region 15, Intermountain West (Southern ID, NV), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well understood.
characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Intermountain West region including southern Idaho and Nevada. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>1</td>
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<tr>
<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages. Total IgE:

**Results Reported in kU/L**

<table>
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<tr>
<th>Age</th>
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Current as of June 14, 2021 12:13 pm CDT   800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 2209

Respiratory Profile, Region 16, Inland Northwest (OR, Central and Eastern WA), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Inland Northwest region including Oregon and central and east Washington Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:
Class IgE kU/L  Interpretation
0        Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive  Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
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</tr>
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Pacific Northwest including the region of Northwestern California, Western Oregon and Washington Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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</tr>
</tbody>
</table>

Reference values apply to all ages. Total IgE:

**Results Reported in kU/L**

<table>
<thead>
<tr>
<th>Age</th>
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</tr>
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<tbody>
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</tr>
<tr>
<td>18 years and older</td>
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</tr>
</tbody>
</table>

**Respiratory Profile, Region 18, Alaska, Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in Alaska
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: Responsible for allergic disease and/or anaphylactic episode
To confirm sensitization prior to beginning immunotherapy
To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
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<td>6</td>
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</tbody>
</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L
**Age** | **Reference interval**
--- | ---
0-5 months | $< \text{ or } =13$
6-11 months | $< \text{ or } =34$
1 and 2 years | $< \text{ or } =97$
3 years | $< \text{ or } =199$
4-6 years | $< \text{ or } =307$
7 and 8 years | $< \text{ or } =403$
9-12 years | $< \text{ or } =696$
13-15 years | $< \text{ or } =629$
16 and 17 years | $< \text{ or } =537$
18 years and older | $< \text{ or } =214$

**Clinical References:**

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RPR19 62065

**Respiratory Profile, Region 19, Puerto Rico, Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in Puerto Rico
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases,
including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages. Total IgE:

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**Respiratory Profile, Region 2, Mid-Atlantic (DC, DE, MD, NC, VA), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because
of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Mid-Atlantic region including the District of Columbia, Delaware, Maryland, North Carolina and Virginia Defining the allergen responsible for eliciting signs and symptoms Identifying allergens Responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages. Total IgE:

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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the South Atlantic region including Georgia, Northern Florida and South Carolina Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in sub-tropic Florida, which is south of Orlando Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Useful For: Assessing sensitization to various inhalant allergens commonly found in the Ohio Valley region including Indiana, Kentucky, Ohio, Tennessee and West Virginia. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Respiratory Profile, Region 6, South Central (AL, AR, LA, MS), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the South Central region including Alabama, Arkansas, Louisiana and Mississippi Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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**Respiratory Profile, Region 7, Northern Midwest (MI, MN, WI), Serum**

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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Northern Midwest region including Michigan, Minnesota, and Wisconsin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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</tr>
<tr>
<td>18 years and older</td>
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</tbody>
</table>

Respiratory Profile, Region 8, Central Midwest (IA, IL, MO), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Central Midwest region including Iowa, Illinois and Missouri Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode Confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3 3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 2224
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive  Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
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<tr>
<td>0-5 months</td>
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**Respiratory Profile, Region 9, Great Plains (KS, ND, NE, SD), Serum**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).
Useful For: Assessing sensitization to various inhalant allergens commonly found in the Great Plains region including Kansas, North Dakota, Nebraska and South Dakota Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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RSVAB 601948  Respiratory Syncytial Virus (RSV) In Situ Hybridization, Technical Component Only

Clinical Information: Respiratory syncytial virus (RSV) causes a wheezing illness that especially affects young children. The virus infects alveolar pneumocytes and induces fusion of multiple cells, creating a "syncytial" multinucleated cell. This RSV probe sequence was designed to identify subgroups...
RSV-A and RSV-B. It has been verified to not cross react with the following viruses in formalin-fixed, paraffin-embedded (FFPE) tissue: adenovirus (ADV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis C virus (HCV), human herpes virus, type 8 (HHV-8), human papillomavirus (HPV) types 6, 11, 16, E6/E7, Helicobacter pylori (H pylori), herpes simplex virus (HSV) types 1 and 2, JC virus (JCV), parvovirus, toxoplasma, and varicella-zoster viruses (VZV).

**Useful For:** Aids in the identification of respiratory syncytial viral infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Respiratory Syncytial Virus (RSV) RNA, Qualitative Real-Time PCR**

**Clinical Information:** This test is used to determine the presence of respiratory syncytial virus (RSV) in a patient's specimen. Organisms may be detected by PCR prior to diagnosis by immunological methods. PCR provides more rapid results than other methods, including culture.

**Reference Values:**
Not Detected

**RET Proto-Oncogene, Full Gene Analysis, Varies**

**Clinical Information:** Mutations in the RET proto-oncogene are associated with 3 distinct, and in rare cases, overlapping clinical syndromes. Multiple endocrine neoplasia type 2 (MEN2): MEN2 is an autosomal dominant cancer syndrome that has classically been divided into 3 subtypes: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). The characteristic features of MEN 2A include medullary thyroid carcinoma (MTC), pheochromocytoma, and primary hyperparathyroidism. MEN 2B is characterized by early-onset MTC, pheochromocytoma, mucosal neuromas, and distinctive facies with enlarged lips. Other features of MEN 2B include enlarged nerves of the gastrointestinal tract (ganglioneuromatosis), marfanoid habitus, hypotonia, and corneal nerve thickening. FMTC has traditionally been diagnosed in families with or more cases of MTC in the absence of pheochromocytoma or parathyroid involvement. Early diagnosis of thyroid cancer and appropriate surgical intervention can prevent metastatic MTC and can reduce the morbidity and mortality associated with MTC. All MEN2 subtypes are inherited in an autosomal dominant inheritance pattern. The majority of MEN2-related mutations occur at conserved cysteine residues within exons 10 and 11. Additional mutations in exons 13, 14, 15, and 16 account for the majority of other MEN2-related RET mutations. Hirschsprung disease (HSCR): HSCR is a congenital disorder of impaired intestinal motility, also known as aganglionic megacolon. Variable lengths of the colon may be affected, resulting in either total aganglionosis, long-segment HSCR, or short-segment HSCR. HSCR affects approximately 1 in 5,000 live births and is resolved via surgical intervention. Hirschsprung disease can result from chromosome abnormalities, single gene disorders (both syndromic and non-syndromic), a combination...
of mutations in multiple genes, and unknown causes. Pathogenic RET variants are considered the most common cause of HSCR cases, though, particularly in families with multiple cases of HSCR and long segment disease. It has been reported that up to 50% of familial cases of HSCR and 3% to 10% of single HSCR cases are due to RET germline mutations. While gain of function mutations in RET are typically associated with MEN2, loss of function mutations have been reported in patients with Hirschsprung disease (HSCR) including full or partial RET gene deletions. In addition to clearly pathogenic RET variants that cause HSCR, additional benign variants in RET (which may not be causative in themselves) confer increased susceptibility to HSCR. Congenital central hypoventilation syndrome (CCHS): CCHS is a congenital disorder of autonomic nervous system dysfunction in which individuals hypoventilate during sleep, and less commonly while awake. While not the primary etiology of disease, RET mutations have been associated with CCHS; in addition, RET mutations may be modifiers of CCHS development in individuals with HSCR. Co-occurrence of HSCR and CCHS is more commonly observed than the co-occurrence of MEN2 with either HSCR or CCHS.

**Useful For:** Confirmation of suspected clinical diagnosis of multiple endocrine neoplasia type A or B, Hirschsprung disease, or congenital central hypoventilation syndrome. Identification of familial pathogenic or likely pathogenic RET mutation to allow for predictive or diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**RTIC 9108**

**Reticulocytes, Blood**

**Clinical Information:** Reticulocytes are immature erythrocytes (RBC) that have been released into the peripheral blood from the bone marrow after extrusion of their nucleus. The reticulocyte contains residual polyribosomes used in the formation of hemoglobin in the developing erythrocyte.

**Useful For:** Assessing erythropoietic bone marrow activity in anemia and other hematologic conditions

**Interpretation:** The reticulocyte count is a measure of the number of RBCs delivered by the bone marrow. It is elevated with active erythropoiesis such as regeneration, and is decreased in hypoplastic or...
deficiency conditions such as vitamin B12 deficiency.

**Reference Values:**

% RETICULOCYTES

1-3 days: 3.47-5.40%
4 days-4 weeks: 1.06-2.37%
5 weeks-7 weeks: 2.12-3.47%
8 weeks-5 months: 1.55-2.70%
6 months-23 months: 0.99-1.82%
24 months-5 years: 0.82-1.45%
6-11 years: 0.98-1.94%
12-17 years: 0.90-1.49%
Adults: 0.60-2.71%

ABSOLUTE RETICULOCYTES

1-3 days: 147.5-216.4 x 10(9)/L
4 days-4 weeks: 51.3-110.4 x 10(9)/L
5 weeks-7 weeks: 51.8-77.9 x 10(9)/L
8 weeks-5 months: 48.2-88.2 x 10(9)/L
6 months-23 months: 43.5-111.1 x 10(9)/L
24 months-5 years: 36.4-68.0 x 10(9)/L
6-11 years: 42.4-70.2 x 10(9)/L
12-17 years: 41.6-65.1 x 10(9)/L
Adults: 30.4-110.9 x 10(9)/L

**Clinical References:**


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**Retinoblastoma Protein (Rb) Immunostain, Tech Only**

**Clinical Information:** Retinoblastoma (Rb) is a phosphoprotein that is expressed in most normal cells and acts as a tumor suppressor by providing a cell cycle checkpoint between G1 and S phases. Loss of nuclear expression of Rb is useful in the identification of neuroendocrine carcinomas and small cell carcinomas. Loss of Rb can also be helpful to differentiate spindle cell lipomas from myofibroblastomas and cellular angiofibromas from other genital stromal lesions.

**Useful For:** Aids in the identification of high grade neuroendocrine carcinomas and small cell carcinomas.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**FRBP 75570**

**Retinol Binding Protein**

**Reference Values:**

1.5 - 6.7 mg/dL

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**RBP24 81783**

**Retinol-Binding Protein, 24 Hour, Urine**

**Clinical Information:** Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues. Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function. Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

**Useful For:** Assessing renal tubular injury or dysfunction Screening for other tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

**Interpretation:** Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

**Reference Values:**

<163 mcg/24 hours

**Clinical References:**


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**RRBP 84447**

**Retinol-Binding Protein, Random, Urine**

**Clinical Information:** Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues. Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubules cells where it is catabolized. Due to
extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function. Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies are also often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that 1 test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

**Useful For:** Assessing renal tubular injury or dysfunction
Screening for other tubular abnormalities
Detecting chronic asymptomatic renal tubular dysfunction

**Interpretation:** Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

**Reference Values:**
<50 years: <130 mcg/g creatinine
> or =50 years: <172 mcg/g creatinine

**Clinical References:**

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**Rheumatoid Factor (RF); IgG, IgA & IgM**

**Interpretation:** The presence of abnormal levels of all three rheumatoid factor (RF) isotypes has a specificity of 99% for Rheumatoid Arthritis. IgA-RF alone can occur in Henoch Schoenlein purpura. RF in any isotype combination may be found in hepatitis C, Sjogren Syndrome, and other chronic infections. Borderline/Equivocal RF results warrant redraw & retesting to confirm.

**Reference Values:**

- Rheumatoid Factor (RF) levels IgG:
  - Negative: <20 EU/mL
  - Borderline/Equivocal: 20-25 EU/mL
  - Positive: >25 EU/mL

- Rheumatoid Factor (RF) levels IgA:
  - Negative: <20 EU/mL
  - Borderline/Equivocal: 20-25 EU/mL
  - Positive: >25 EU/mL

- Rheumatoid Factor (RF) levels IgM:
  - Negative: <10 IU/mL
  - Borderline/Equivocal: 10-12.5 IU/mL
  - Positive: >12.5 IU/mL

**Clinical Information:** Rheumatoid factors (RF) are a heterogeneous group of autoantibodies that are associated with the diagnosis of rheumatoid arthritis (RA), but can also be found in other...
inflammatory rheumatic and nonrheumatic conditions. They can also be detected in some healthy individuals 60 years and older. Despite being nonspecific, the detection of RF or anti-citrullinated protein (anti-CCP) antibody, is part of the 2010 diagnosis criterion of the American College of Rheumatology for classification of RA. More than 75% of patients with RA have an IgM antibody to IgG. The titer of RF correlates poorly with disease activity, but those patients with high titers tend to have more severe disease and, thus, a poorer prognosis than do sero-negative patients. A meta-analysis compared the sensitivity and specificity of IgM RF versus anti-CCP antibody. For IgM RF, the sensitivity was 69% (CI, 65%-73%) and specificity was 85% (CI, 82%-88%). For comparison, the sensitivity for anti-CCP antibody was 67% (95% CI, 62%-72%) and 95% (CI, 94%-97%).(1) Both anti-CCP and RF are useful in the diagnosis of RA, and the use of both tests has been shown to increase diagnostic sensitivity.(2)

Useful For: Diagnosis and prognosis of rheumatoid arthritis

Interpretation: Positive results are consistent with, but not specific for, rheumatoid arthritis.

Reference Values:


Rhizopus nigricans, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Rhizopus nigricans Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Rhodotorula IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strongly Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Rhubarb (Rheum rhaponticum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strongly Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Riboflavin (Vitamin B2), Plasma**

**Clinical Information:** There are 3 principle vitamin B2-active flavins found in nature riboflavin, riboflavin 5-phosphate (flavin mononucleotide: FMN), and riboflavin-5’-adenosyl-diphosphate (flavin adenine dinucleotide: FAD). In biological tissues, FMN and FAD serve as prosthetic units for a large variety of flavoproteins, which are hydrogen carriers in oxidation-reduction processes. Dietary deficiency of riboflavin (ariboflavinosis) is characterized by sore throat, cheilosis (lesions on the lips), angular stomatitis (lesions on the angles of the mouth), glossitis (fissured and magenta-colored tongue), corneal vascularization, dysesthesia (red, scaly, greasy patches on the nose, eyelids, scrotum, and labia), and normocytic, normochromic anemia. Severe riboflavin deficiency may affect the conversion of vitamin B6 to its coenzyme, as well as conversion of tryptophan to niacin. Riboflavin has a low level of toxicity and no case of riboflavin toxicity in humans has been reported. The limited absorptivity of riboflavin and its ready excretion in the urine normally preclude a health problem due to increased intake of riboflavin.

**Useful For:** Evaluation of individuals who present the signs of ariboflavinosis

**Interpretation:** Low concentrations in the blood plasma are indicative of nutritional deficiency. Concentrations below 1 mcg/L are considered significantly diminished. Marginally low levels probably represent nutritional deficiency that should be corrected.

**Reference Values:**

Ribosome P Antibodies, IgG, Serum

Clinical Information: The 80S mammalian ribosome is composed of approximately equal amounts of protein and RNA. The larger 60S subunit contains 3 acidic phosphoproteins, PO, P1, and P2 with molecular masses of 38 kDa, 19 kDa, and 17 kDa, respectively. The major immunoreactive epitope of these 3 autoantigens is found within 22 consecutive amino acids of the carboxy terminus of these 3 highly conserved proteins. It has been known for some time that sera from some patients with lupus erythematosus (LE) react with ribosomal protein antigens. Studies performed with synthetic peptide antigens revealed that reactivity detected by immunoprecipitation and by immunofluorescence methods in sera from LE patients was directed at the above mentioned epitope. Antibodies to ribosome P proteins are considered highly specific for LE, and have been reported in patients with central nervous system (CNS) involvement and so called "lupus psychosis." The reported frequency of antibodies to ribosome P protein autoantigens in patients with LE is approximately 12%. Since patients with LE may manifest signs and symptoms of CNS diseases including neuropsychiatric symptoms, the presence of antibodies to ribosome P protein may be useful in the differential diagnosis of such patients. Other causes of CNS symptoms in patients with LE include thrombosis with or without antibodies to phospholipid antigens and iatrogenic effects from treatment with corticosteroid drugs.

Useful For: As an adjunct in the evaluation of patients with lupus erythematosus (LE) Aids in the differential diagnosis of neuropsychiatric symptoms in patients with LE

Interpretation: A positive result is consistent with the diagnosis of lupus erythematosus, and may indicate the presence of central nervous system involvement.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


Rice IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of
food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Rice, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rice Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
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<td>50.0-99.9</td>
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</tr>
</tbody>
</table>
| 6     | > or =100| Strongly positive Reference values apply to all ages.


Rifampin Level (PKRIF)

Interpretation: The target range for mycobacterial infections is 8 to 24 mcg/mL 2 hours after oral dose or 2 hours after the end of intravenous infusion. Samples drawn later than 2 hours after the dose will often display concentrations below the stated range. Rifampin generally should be given as a single daily dose. If the patient is receiving 2 small daily doses, consider combining the doses and rechecking...
the concentration. Rifampin absorption may be reduced by food. Take on an empty stomach if possible. Rifampin does not have clear concentration-related toxicity and most patients tolerate concentrations above the stated range without difficulty. Hepatic dysfunction may produce elevated rifampin concentrations. Rifampin concentrations greater than 50% above the range may warrant a dose reduction of 150 to 300 mg. If the time of the dose and the blood draw were not accurately recorded, accurate interpretation of the concentration is not possible.

Reference Values:
mcg/mL

ROMA2 46917 Risk Score, if Postmenopausal, Serum

Reference Values:
Only orderable as part of a profile. For more information see ROMA / Ovarian Malignancy Risk Algorithm.

ROMA1 46916 Risk Score, if Premenopausal, Serum

Reference Values:
Only orderable as part of a profile. For more information see ROMA / Ovarian Malignancy Risk Algorithm.

FRISP 91105 Risperidone (Risperdal) and 9-Hydroxyrisperidone

Reference Values:
Units: ng/mL

Expected steady state concentrations of risperidone and 9-hydroxyrisperidone (combined total) in patients receiving recommended daily dosages: 10 - 120 ng/mL.

RIVAR 65847 Rivaroxaban, Anti-Xa, Plasma

Clinical Information: Rivaroxaban, an oral anticoagulant that directly inhibits factor Xa, has been approved by the FDA for prophylaxis of thrombosis in atrial fibrillation and surgical patients and treatment of venous thromboembolism (VTE). Unlike warfarin, it does not require routine therapeutic monitoring. However, in selected clinical situations, measurement of drug level would be useful (eg, renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight). Plasma Concentrations of Rivaroxaban in Patient Populations Studied(1) Patient population/clinical setting Rivaroxaban dose C-min (ng/mL)* trough plasma conc (predose) C-max (ng/mL)** peak plasma conc (2-4 hours postdose) VTE prevention after total hip replacement surgery 10 mg once daily 9 (1-38) 125 (91-196) DVT treatment (continued treatment) 20 mg once daily 26 (6-87) 270 (189-419) Stroke prevention in patients with non-valvular AF (CR-CL > or =50 mL/min) 20 mg once daily 44 (12-137) 249 (184-343) Stroke prevention in patients with non-valvular AF (CR-CL 30-49 mL/min) 15 mg once daily 57 (18-136) 229 (178-313) Secondary prevention in patients with acute coronary syndrome 2.5 mg twice daily 17 (6-37) 46 (28-70) Median (5th-95th percentile) *Defined as samples collected 20-28 hours after dosing **Defined as samples collected 2-4 hours after dosing AF-atrial fibrillation, CR-CL-creatinine clearance, DVT-deep vein thrombosis, VTE-venous thromboembolism

Useful For: Measuring rivaroxaban concentration in selected clinical situations (eg, renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age and extremes of body weight)

Interpretation: The lower limit of detection of this assay is 4 ng/mL. Therapeutic reference ranges
RNA Polymerase III Antibodies, IgG, Serum

Clinical Information: Systemic sclerosis is a multisystem connective tissue (systemic rheumatic) disease characterized by fibroblast dysfunction leading to fibrosis of the skin and internal organs, microvascular injury leading to tissue hypoxia, and an autoimmune response manifested by production of autoantibodies. (1,2) The severity of the disease is highly variable among individual patients. Limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis have been recognized as distinct subsets, with worse survival for those with the diffuse form. (2) Clinical features of CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) can be seen in both limited cutaneous and diffuse cutaneous forms but, overall, are associated with a better prognosis. (2) Several disease-specific and mutually exclusive autoantibodies have been identified that are helpful in both diagnosis and disease classification. Centromere and topoisomerase I (Scl 70) autoantibodies are associated with limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis, respectively. (3) RNA polymerase III is a complex, 16-subunit enzyme directing transcription of small, stable nontranslated RNA genes: tRNA, 5S rRNA, Alu RNA, U6 snRNA, and 7SK snRNA genes. The immunodominant epitope for autoantibodies with anti-RNA polymerase I/III specificity has been identified on the RNA polymerase-specific subunit RPC155. (4) Autoantibodies to RNA polymerase III antigen are found in 11% to 23% of patients with systemic sclerosis. (1,4) Systemic sclerosis patients who are positive for RNA polymerase III antibodies form a distinct serologic subgroup and usually do not have any of the other antibodies typically found in systemic sclerosis patients such as anticentromere or anti-Scl70. (1) Numerous studies have shown that systemic sclerosis patients with anti-RNA polymerase III have an increased risk of the diffuse cutaneous form of scleroderma, with a high likelihood of skin involvement and hypertensive renal disease. (1,4)

Useful For: Evaluating patients suspected of having systemic sclerosis, when used in conjunction with centromere and Scl70 antibodies Providing diagnostic and prognostic information in patients with systemic sclerosis

Interpretation: A positive result supports a possible diagnosis of systemic sclerosis (see Cautions). This autoantibody is strongly associated with diffuse cutaneous scleroderma and with an increased risk of acute renal crisis. A negative result indicates no detectable IgG antibodies to RNA polymerase III, but does not rule out the possibility of systemic sclerosis (11%-23% sensitivity). (1,4)

Reference Values: <20.0 U (negative) 
20.0-39.9 U (weak positive)
40.0-80.0 U (moderate positive)
> 80.0 U (strong positive)

**Clinical References:**

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### RNP Antibodies, IgG, Serum

**Clinical Information:** RNP (also called nRNP and U1RNP) is a small nuclear ribonucleoprotein that contains 3 protein autoantigens (called A, C, and 68 kD). Sera that contain RNP antibodies react predominately with the A and 68-kD autoantigens. Antibodies to RNP occur in approximately 50% of patients with lupus erythematosus (LE) and in patients with other connective tissue diseases, notably mixed connective tissue disease (MCTD). MCTD is characterized by high levels of RNP antibodies without detectable Sm (Smith) or double-stranded DNA (dsDNA) antibodies. MCTD resembles LE but is not accompanied by renal involvement. RNP is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENA). The other ENAs are SS-A/Ro, SS-B/La, and Sm. Each ENA is composed of 1 or more proteins associated with small nuclear RNA species (snRNP) ranging in size from 80 to approximately 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, MCTD, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive. Testing for RNP antibodies is not useful in patients without demonstrable antinuclear antibodies.

**Interpretation:** A positive result for RNP antibodies is consistent with a connective tissue disease. Although strongly associated with connective tissue diseases, RNP antibodies are not considered a “marker” for any particular disease except in the following situation: when found in isolation (ie, dsDNA antibodies and Sm antibodies are not detectable), a positive result for RNP antibodies is consistent with the diagnosis of mixed connective tissue disease.

**Reference Values:**
- < 1.0 U (negative)
- > or = 1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**

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### ROMA Score (Ovarian Malignancy Risk Algorithm), Serum

**Clinical Information:** Women with ovarian cancer symptoms and adnexal masses present primarily to gynecologists, primary care physicians, or general surgeons. Triage guidelines from the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists recommend referral of women with a pelvic mass at high risk for ovarian cancer to gynecologic oncologists. Specialized treatment improves patient outcomes resulting in fewer complications and better survival rates when compared to patients treated by surgeons less familiar with the management of ovarian cancer.
The risk of ovarian malignancy algorithm (ROMA) incorporates cancer antigen 125 (CA125), human epididymal protein 4 (HE4), and menopausal status to assign women that present with an adnexal mass into a high-risk or low-risk group for finding an ovarian malignancy. ROMA is indicated for women who meet the following criteria: older than age 18, presenting with an adnexal mass for which surgery is planned, and who have not yet been referred to an oncologist. ROMA must be interpreted in conjunction with clinical and radiological assessment.

**Useful For:** Risk assessment for finding an ovarian malignancy during surgery in women who present with an adnexal mass. The test is not intended as a screening or stand-alone diagnostic assay for ovarian cancer.

**Interpretation:** In premenopausal women, a risk of ovarian malignancy algorithm (ROMA) value of 1.14 or greater indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 1.14 indicates a low risk of finding epithelial ovarian cancer at surgery. In postmenopausal women, a ROMA value of 2.99 or greater indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 2.99 indicates a low risk of finding epithelial ovarian cancer at surgery. The use of these cut-points provides a 75% specificity and sensitivity of 84% in patients with stage I-IV epithelial ovarian cancer.

**Reference Values:**

Males: Not applicable

Females:

- HUMAN EPIDIDYMIS PROTEIN \( \leq 140 \) pmol/L
- CANCER ANTIGEN 125 <46 U/mL
- ROMA SCORE
  - Premenopausal: <1.14 (low risk)
  - Postmenopausal: <2.99 (low risk)

**Clinical References:**


**FROPI**

**Ropivacaine, Serum/Plasma**

**Reference Values:**

Reporting limit determined each analysis.

Following epidural administration 10 mg/hr, 20 mg/hr and 30 mg/hr, mean plasma concentration of 0.39, 0.88, 1.19 mcg/mL at 21 hours respectively.

Bolus I.V. administration 84 mg/70 kg and 131 mg/70 kg, peak plasma concentrations of 1.1 and 1.7 mcg/mL at 2 minutes respectively.

**ROTA**

**Rotavirus Antigen, Feces**

**Clinical Information:** Rotavirus is a major cause of nonbacterial gastroenteritis, especially in infants and very young children (6 months-2 years of age) who have not received the rotavirus vaccine. Infection may be entirely asymptomatic or produce a spectrum of disease ranging from mild gastroenteritis to severe diarrhea and vomiting with dehydration. Infection usually begins acutely and lasts for 4 to 8 days. In temperate climates, rotaviral infections are seasonal; they peak in frequency during the winter months and are uncommon during the summer. Rotaviral gastroenteritis is, therefore, sometimes called "winter vomiting disease." Infection is more likely to be symptomatic in preterm
infants, immunosuppressed patients, and elderly individuals, especially those living in nursing homes or other confined quarters. In other children and adults, rotavirus infections are usually subclinical and may be associated with asymptomatic shedding of rotavirus in the feces. Rapid and accurate detection of rotavirus antigens in fecal specimens may lead to better patient management, particularly in hospitalized or institutionalized patients.

**Useful For:** Investigation of patients with diarrhea, particularly infants, the elderly, and immunocompromised patients Investigation of nosocomial diarrhea

**Interpretation:** Peak viral counts are reported to occur on days 3 to 5 after onset of symptoms. The virus is eliminated from the infected individual within a few days following acute infection. Specimens collected 8 days or more after onset of symptoms may not contain enough rotavirus antigen to produce a positive reaction. A prolonged carrier state has been recognized with rotavirus infection. The rate of positive test results may vary due to age, weather, seasonal factors, geographic location, and the general health environment for the group under study. See Laboratory Testing for Infectious Causes of Diarrhea Algorithm in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Reference Values:**

**Negative**


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**MARS 82701 Rough Marsh Elder, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rough marsh elder Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
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<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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</tr>
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<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Rough Pigweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rough pigweed Defining the allergens responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
</table>
| 6     | > or =100| Strongly positive Reference values apply to all ages.


Rubella Antibodies, IgG, Serum

Clinical Information: Rubella (German or 3-day measles) is a member of the Togavirus family and
humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. (1) Infection is generally mild, self-limited, and characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. (2) Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects. (3) The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. (1) A total of 4 cases of rubella were reported to the Centers for Disease Control and Prevention in 2011 without any cases of congenital rubella syndrome. (4) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (www.cdc.gov/rubella). However, immunity may wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella.

**Useful For:** Determination of immune status to the rubella virus

**Interpretation:** Positive: Antibody index (AI) value of 1.0 or higher -The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. -The presence of detectable IgG-class antibodies indicates immunity to the rubella virus through prior immunization or exposure. Individuals testing positive are considered immune to rubella infection. Equivocal: AI value 0.8-0.9 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value of 0.7 or lower The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the rubella virus.

**Reference Values:**

Vaccinated: positive (> or =1.0 AI)

Unvaccinated: negative (< or =0.7 AI)

Reference values apply to all ages.

**Clinical References:**


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**Rubeola (Measles) Antibodies, IgG and IgM, Spinal Fluid**

**Clinical Information:** Measles is a serious and highly contagious disease that can be a leading cause of death where nutrition and sanitation are limited. Onset begins with cough, fever, and lymphadenopathy approximately 2 weeks after exposure. Diagnosis is usually made when the rash appears. Koplik spots may be seen earlier on the buccal mucosa. Complications of measles may develop in children who appear to have normal immune functions. Persistent infection of the central nervous system with measles virus is recognized to cause the disease subacute sclerosing panencephalitis (SSPE). SSPE is a rare, late complication of measles with an incidence of approximately 1 per 100,000 cases. SSPE is a progressive, usually fatal disease that occurs most often in children between the ages of 5 and 14. The onset is insidious and progressive. The incubation period from acute measles to onset of neurological symptoms varies from several months to many years. One of the most useful diagnostic tests involves the measurement of measles-specific antibodies in the cerebrospinal fluid (CSF) of patients with SSPE. Levels of antibody are significantly elevated in the CSF of SSPE patients compared to those without the disease.

**Useful For:** Diagnosis of central nervous system infection with rubeola (measles) virus and/or subacute sclerosing panencephalitis

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may
suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection. Patients with subacute sclerosing panencephalitis have serum antibody titers which are 10 to 100 times higher than those seen in late convalescent-phase sera. More importantly, there is pronounced local production of oligoclonal measles virus antibodies in the central nervous system.

**Reference Values:**

<table>
<thead>
<tr>
<th>IgG</th>
<th>&lt;1:5</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>&lt;1:10</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:**

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**RUFI 63030**

**Rufinamide, Serum**

**Clinical Information:** Rufinamide is a new antiepileptic drug (AED) approved by the Food and Drug Administration as add-on treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 4 years of age or older and for the treatment of focal seizures in adults and adolescents. Its mechanism of action is not completely understood, but it is believed to work by prolonging the inactive state of sodium channels and therefore limiting excessive firing of sodium-dependent action potentials. The most commonly observed side effects are headache, dizziness, fatigue, somnolence, and nausea.

**Useful For:** Monitoring serum rufinamide concentrations, assessing compliance, and adjusting dosage in patients receiving other drugs which interact pharmacokinetically with rufinamide (ie, drugs that induce liver CYP3A4 enzymes) and may be helpful in who are receiving hemodialysis

**Interpretation:** The reference interval is broad and represents the concentrations observed to be associated with the greatest drug efficacy without side effects or toxicity.

**Reference Values:**

5.0-30.0 mcg/mL

**Clinical References:**

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**RUSS 82681**

**Russian Thistle, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to russian thistle Defining the allergen responsible
for eliciting signs and symptoms 

Identifying allergens:
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
- To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference** values apply to all ages.


### Rye Food IgG

**Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Rye Grass, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rye grass Defining the allergen responsible for
eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**Rye, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to rye Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<td>5</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


**2SC**

S-(2-Succinyl)-Cysteine (2SC) Immunostain, Technical Component Only

**Clinical Information:** A subset of aggressive renal tumors have pathogenic alterations of fumarate hydratase (FH) that do not result in the loss of FH expression. Typically FH alterations are associated with aberrantly high levels of S-(2-succino)-cysteine (2SC) expression observed in the nucleus. FH and 2SC immunohistochemistry assays may be used in combination to identify these pathogenic conditions. This is useful in the diagnosis of renal cell carcinomas, cutaneous and uterine leiomyomas, that occur secondary to somatic or germline (hereditary leiomyomatosis and renal cell cancer: HLRCC syndrome) alterations of the FH gene.

**Useful For:** Identification of high levels of aberrant S-(2-succino)-cysteine (2SC), secondary to pathogenic alterations of the fumarate hydratase (FH) gene

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**S-100 Immunostain, Technical Component Only**

Current as of June 14, 2021 12:13 pm CDT

800-533-1710 or 507-266-5700 or mayocliniclabs.com

Page 2246
**Clinical Information:** S-100 expression is seen in cartilaginous tumors, myoepithelial tumors, Schwann cells and neural tumors, Langerhans cell proliferations, benign and malignant melanocytes, clear cell sarcoma, and some carcinomas (particularly of the breast). S-100 staining occurs both in the nucleus and cytoplasm.

**Useful For:** Aids in the identification of various neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PTHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**F100B**

**S-100B Protein, Serum**

**Reference Values:**
0–96 ng/L

This assay is performed using the CanAg S100 Enzyme Immunoassay. Results obtained with different assay methods or kits cannot be used interchangeably.

**SSCTU**

**S-Sulfocysteine Panel, Urine**

**Clinical Information:** Urine s-sulfocysteine is elevated in 2 disorders with similar clinical phenotypes: molybdenum cofactor deficiency (MoCD) and isolated sulfite oxidase deficiency. Molybdenum is an important trace element that is biosynthesized into an important cofactor, which is essential for the proper functioning of the enzymes xanthine oxidase, sulfite oxidase, and aldehyde oxidase in addition to nitrogenases and nitrate reductase. Four genes are important in mediating the biosynthetic pathway to create molybdenum cofactor: MOCS1, MOCS2, MOCS3, and GPHN (gephyrin). The 3 clinical types of MoCD are autosomal recessive diseases resulting from 2 pathogenic variants in the respective causative gene. MoCDs result in a progressive neurodegenerative disease that manifests with seizures and brain abnormalities in the first weeks to months of life. The most common type of MoCD is MoCD A, caused by variants in MOCS1 and resulting in neonatal or infantile onset seizures and postnatal encephalopathy with rapidly progressive neurodegeneration. Infants with MoCD B (MOCS2 or MOCS3), and C (GPHN) have all been reported but are rare. Infants with MoCD have increased s-sulfocysteine and hypoxanthine and decreased uric acid concentrations in urine. Treatment for MoCD A only is available via clinical trial with cyclic pyranopterin monophosphate infusion and is most effective when initiated early. Isolated sulfite oxidase deficiency (ISOD) is an autosomal recessive
disorder caused by deficiency of the enzyme sulfite oxidase, which results in progressive neurodegenerative disease in most cases. ISOD is the result of pathogenic variants in the SUOX gene. ISOD is a spectrum of disease ranging from severe, early onset disease that appears in the first days of life with seizures, feeding issues, and neurologic issues causing abnormal muscle tone, to mild, later onset disease manifesting after 6 months of age with developmental delay or regression, movement issues, which can be episodic, and ectopia lentis in some cases. Infants with ISOD have increased s-sulfocysteine and normal hypoxanthine concentrations in urine. Treatment is largely symptomatic, with medication for seizures and movement/neurologic issues. Unfortunately, no treatment for the underlying metabolic defect is currently available. Prevalence is unknown, but ISOD is likely underdiagnosed. Hereditary xanthinuria results in renal stones, and less commonly muscle pain and cramping, caused by accumulation of xanthine that forms crystals in the kidneys and muscle tissue. There are 2 types of hereditary xanthinuria: type I caused by deficiency of xanthine dehydrogenase resulting from pathogenic variants in the XDH gene, and type II caused by deficiency of molybdenum cofactor sulfurase resulting from variants in the MOCOS gene. Individuals with xanthinuria have increased xanthine and decreased uric acid concentrations in urine. The incidence of both types of hereditary xanthinuria is about 1 in 69,000 individuals.

**Useful For:** Diagnosis of molybdenum cofactor deficiency, isolated sulfite oxidase deficiency and hereditary xanthinuria Monitoring patients with molybdenum cofactor deficiency or isolated sulfite oxidase deficiency on treatment

**Interpretation:** Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies, and a phone number of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

| S-Sulfocysteine panel, urine Reference values (all results reported as mmol/mol creatinine) |
|-----------------------------------------------|---------------------------------|----------------|----------------|----------------|
| 0-3 years | 4-6 years | 7-12 years | 13-18 years | >18 years |
| Hypoxanthine | < or =65 | < or =30 | < or =30 | < or =30 |
| Xanthine | < or =54 | < or =21 | < or =35 | < or =15 |
| Uric Acid | 350-2500 | 200-2000 | 200-1400 | 150-700 |
| S-Sulfocysteine | < or =11 | < or =5 | < or =5 | < or =5 |

**Clinical References:**

**Safflower (Carthamus tinctorius) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Â– 0.69 Low Positive 2 0.70 Â– 3.49 Moderate Positive 3 3.50 Â– 17.49 Positive 4 17.50 Â– 49.99 Strong Positive 5 50.00 Â– 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**Sage (Artemisia spp.) IgE**
**Interpretation:**
Class IgE (kU/L) Comment
0 <0.35 Below Detection
1 0.35 – 0.69 Low Positive
2 0.70 – 3.49 Moderate Positive
3 3.50 – 17.49 Positive
4 17.50 – 49.99 Strong Positive
5 50.00 – 99.99 Very Strong Positive
6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Salicylate, Serum**

**Clinical Information:** Therapeutic salicylates include, among others, salicylic acid, sodium salicylate, methyl salicylate (oil of wintergreen), and acetylsalicylic acid (aspirin). Aspirin is an analgesic, antipyretic, anti-inflammatory drug contained in a large number of preparations. Aspirin is rapidly hydrolyzed by hepatic and blood esterases to the pharmacologically active intermediate, salicylic acid, which has a dose-dependent serum half-life ranging from 3 to 20 hours. Stimulation of the respiratory center in the central nervous system and uncoupling of oxidative phosphorylation are direct effects of salicylate that lead to many of the toxic symptoms observed in overdose situations. Symptoms of salicylate toxicity can include nausea, vomiting, tinnitus, headache, hyperpnea, confusion, hyperthermia, slurred speech, and convulsions. Acid-base disturbances such as compensated respiratory alkalosis (mild toxicity) and metabolic acidosis with increased anion gap (severe toxicity) are commonplace.

**Useful For:** Assessing toxicity This test is not useful for assessing low-dose aspirin therapy

**Interpretation:** Therapeutic concentrations for antipyretic/analgesic are 3.0 to 10.0 mg/dL, while concentrations between 1.5 and 30 mg/dL are for anti-inflammatory effect and treatment of rheumatic fever. Toxic concentrations are 50.0 mg/dL or higher.

**Reference Values:**
Therapeutic: <30.0 mg/dL
Critical value: > or =50.0 mg/dL

**Clinical References:**
2. Medical Toxicology, Third edition, Edited by RC Dart. 2004 pp 1811

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**SALL4 Immunostain, Technical Component Only**

**Clinical Information:** SALL4 is a zinc-finger transcriptional factor. It is required for the maintenance of embryonic stem cell pluripotency by regulating OCT4 transcription. Staining for SALL4 is useful in distinguishing germ cell tumors from carcinomas, lymphomas, and melanomas.

**Useful For:** Aids in the identification of germ cell tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
3. Cao D, Humphrey P, and Allan R: SALL4 is a novel sensitive and specific marker for metastatic germ
Salmon IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Salmon, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to salmon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<tr>
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<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's
Salmonella Culture, Feces

**Clinical Information:** Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Salmonella species cause disease in 2 broad categories-gastroenteritis, and typhoid (or paratyphoid) fever (eg, Salmonella enterica subspecies enterica serovar Typhi, Salmonella enterica subspecies enterica serovar Paratyphi A, Salmonella enterica subspecies enterica serovar Paratyphi B [tartrate negative], and Salmonella enterica subspecies enterica serovar Paratyphi C). In the United States, gastroenteritis is most common clinical presentation.

**Useful For:** Determining whether Salmonella species may be the cause of diarrhea Reflexive testing for Salmonella species from nucleic acid amplification test-positive feces This tests is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

**Interpretation:** The growth of Salmonella species identifies a potential cause of diarrhea.

**Reference Values:**
No growth of pathogen

**Clinical References:**

Sandhoff Disease, HEXB Gene, Full Gene Analysis, Varies

**Clinical Information:** Sandhoff disease is an autosomal recessive lysosomal storage disorder resulting from deficiencies of hexosaminidase A and hexosaminidase B isoenzymes caused by autosomal recessive pathogenic variants in HEXB. These isoenzymes are dimers, which differ in their subunit composition. Hexosaminidase A is a heterodimer comprised of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer consisting of 2 beta subunits (beta-beta). HEXB gene alterations impact the levels of both hexosaminidase A and hexosaminidase B enzymes and result in defective lysosomal degradation and excessive accumulation of GM2 ganglioside. This causes the clinical symptomology observed in Sandhoff disease. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Sandhoff disease often presents between 2 and 10 years of age with ataxia and clumsiness. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Sandhoff disease often presents between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death typically occurs 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Sandhoff disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between individuals.
and within families. Hexosaminidase A and total enzyme activity testing in serum (NAGS / Hexosaminidase A and Total Hexosaminidase, Serum) or leukocytes (NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes) is the recommended first-tier test for individuals with suspected Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease, and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies.

**Useful For:** Follow up for abnormal biochemical results suggestive of Sandhoff disease Establishing a molecular diagnosis for patients with Sandhoff disease Identifying variants within genes known to be associated with Sandhoff disease, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**SARCP 606427**

**Sarcoma Targeted Gene Fusion/Rearrangement Panel, Next-Generation Sequencing, Tumor**

**Clinical Information:** Molecular analysis of biomarkers is increasingly being utilized in oncology practices to support and guide diagnosis, prognosis, and therapeutic management of patients. Chromosomal translocations, interstitial deletions, and inversions that lead to gene fusions are common in various sarcomas such as Ewing sarcoma and rhabdomyosarcoma. This next-generation sequencing assay is used to detect specific gene fusions to assist in the diagnosis of sarcomas. See Sarcoma Targeted Gene Fusion Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Diagnosing specific soft tissue and bone tumors (sarcoma) based on the observed gene fusions (eg, PAX3/FOXO1 gene fusion observed in alveolar rhabdomyosarcoma, EWSR1-FLI1 gene fusion for Ewing's sarcoma, SS18-SSX1/2 gene fusion for synovial sarcoma)

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

Sardine (Pilchard), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sardine (pilchard) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

Clinical References: Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry’s Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
SARS-CoV-2 Neutralizing Antibody

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. The incubation period for COVID-19 ranges from 3 to 14 days. Typically, immunocompetent individuals with COVID-19 develop detectable antibodies against SARS-CoV-2 approximately 8 to 11 days following onset of symptoms or vaccination. Patients tested prior to this time may be negative for SARS-CoV-2 antibodies.

Useful For: Detection of specific neutralizing antibodies capable of inhibiting SARS-CoV-2-virus.

Interpretation: POSITIVE: SARS-CoV-2 neutralizing antibodies detected. Results suggest recent or prior infection with SARS-CoV-2 or vaccination against SARS-CoV-2, resulting in the generation of neutralizing antibodies against the virus. Correlation with epidemiologic risk factors and other clinical and laboratory findings is recommended. Serologic results should not be used to diagnose recent SARS-CoV-2 infection. NEGATIVE: No neutralizing antibodies to SARS-CoV-2 detected. Negative results may occur in samples collected too soon following infection or immunization, in immunosuppressed patients, or in some individuals with prior mild illness. If there is a high suspicion of recent SARS-CoV-2 infection or recent vaccination, re-testing is recommended after 5-7 days. Follow-up testing with a molecular test is recommended in symptomatic patients (https://www.bioiq.com/resources/covid-19-testing/ts). This test should not be used to exclude active/recent SARS-CoV-2 infection. INDETERMINANT: No determination regarding the presence or absence of neutralizing antibodies can be made. Re-testing is recommended after 5-7 days. VIRUS NEUTRALIZING TITER (VNT): Level of anti-SARS-CoV-2 neutralizing antibodies. Only positive results will have a value reported. Limit of detection (LOD) is 32 VNT. The reference chart below indicates how VNT values compare to a plaque reduction neutralization test 50% (PRNT50) titers against a BSL3 SARS-CoV-2 clinical isolate. VNT PRNT50% < 32 (LOD) < 1:40 32 to 40 1:40 41 to 80 1:80 81 to 180 1:160 181 to 400 1:320 401 to 800 1:640 801 to 1600 1:1280 1601 to 2400 1:2560 >2400 >1:2560

Reference Values:
Negative

SATB2 Immunostain, Technical Component Only

Clinical Information: Special AT-rich sequence binding protein 2 (SATB2) is a transcription factor that regulates gene expression through chromatin remodeling. SATB2, when used in combination with the marker Keratin 20, may identify more than 95% of colorectal carcinoma. It may also be used to differentiate rectal neuroendocrine tumors from other neuroendocrine tumors of the gastrointestinal tract.

Useful For: Identification of colorectal carcinoma and rectal neuroendocrine tumors

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FSCA6 91588  
**SCA 6 (CACNA1A) Repeat Expansion**  
**Reference Values:**  
A final report will be attached in MayoAccess.

FSCA1 91585  
**SCA 1 (ATXN1) Repeat Expansion**  
**Clinical Information:** Detects CAG triplet repeat expansion in the SCA1 gene. Typical Presentation: Ataxia, poor coordination of hand, speech and eye movements, uncoordinated and unsteady gait.  
**Reference Values:**  
A final report will be attached in MayoAccess.

FSCA3 91587  
**SCA 3 (MJC/ATXN3) Repeat Expansion**  
**Clinical Information:** Hereditary ataxias are a group of heterogeneous neurological disorders predominantly characterized by balance issues, progressive incoordination of gait and limbs, speech and eye movements (2, 3). Additional neurologic and systemic symptoms may be present based on the particular subtype (3). The overall prevalence of hereditary ataxias varies depending on the population but is estimated to be 1-9:100,000 (3). Hereditary ataxias may be broken down into subtypes based on the mode in inheritance. Autosomal dominant ataxias are a clinically diverse group of disorders that consist of spinocerebellar ataxias (SCAs), episodic ataxias (EA), and some complex forms of ataxia (3). Autosomal recessive ataxias are also clinically heterogeneous but typically characterized by areflexia, peripheral sensorimotor neuropathy (often with loss of the sense of proprioception and vibration) and non-neurologic symptoms (2, 3). Repeat expansions of CAG in the ATXN3 gene have been associated with spinocerebellar ataxia-3 (SCA3), also known as Machado Joseph disease (MJD). This disorder is characterized by eye lid retraction and infrequent blinking leading to a â€œstaring eyesâ€• phenotype, ophthalmoparesis, and impaired speech and swallowing (4). Other associated features including peripheral neuropathy, dystonia, and distal amyotrophy with areflexia may be present to varying degrees depending on the size of the repeat length (larger repeats being associated with more severe phenotypes) (4, 5). Age of onset follows an inverse relationship with the number of CAG repeats in the abnormal allele (4). Cases of SCA3 may exhibit anticipation from one generation to the next (4).  
**Reference Values:**  
SCA3 CAG Repeat Ranges:  
- Normal: < = 44  
- Borderline 45 - 59  
- Positive > = 60  

SCLE 82716  
**Scale, IgE, Serum**  
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to scallop Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Scallop, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to scallop Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Schistosoma Exam, Random, Urine**

**Clinical Information:** Schistosomiasis is an infection caused by several species of trematodes (flukes) in the genus Schistosoma. The adult worms of Schistosoma haematobium inhabit the venous plexus of the bladder and produce eggs that are typically passed in the urine. Peak egg excretion occurs between noon and 3 p.m. Identification of characteristic eggs in urine is diagnostic for infection with this organism.

**Useful For:** Aiding in the diagnosis of schistosomiasis infections involving the urinary tract

**Interpretation:** A positive result indicates the presence of Schistosoma species ova in urine. A negative result does not rule out the presence of Schistosoma species since ova may be present at levels below the detection limits of this assay, or infection may not involve the urinary tract.

**Reference Values:**

- Negative
- If positive, organism identified


**Schistosoma species Antibody, IgG, Serum**

**Clinical Information:** Schistosoma species (class Trematoda) are flukes, characterized by their flat, leaf-like morphology as adults, and use of gastropod mollusks (eg, snails) as an intermediate host. The schistosomes are also referred to as the “blood flukes,” of which there are 5 species known to infect
humans: Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma mekongi, and Schistosoma intercalatum. Among these S. mansoni, S. japonicum and S. haematobium are most common. These species have a defined geographic distribution, with S. mansoni occurring throughout sub-Saharan Africa, the Middle East, and islands in the Caribbean; S. haematobium found in much of the African continent and the Middle East; and S. japonicum localized to China, Indonesia, and the Philippines. Humans are definitive hosts for all of the Schistosoma species except for S. japonicum, and infection begins with skin penetration of cercariae in contaminated water sources. The cercariae shed their bifurcated tails, becoming schistosomulae and migrate through the vascular system to the lungs, heart, and the portal venous system in the liver. There they mature to adults, pair off and migrate to the mesenteric venules of the bowel and rectum (S. mansoni, S. japonicum) or venus plexus of the bladder (S. haematobium). Females will shed eggs, which are moved progressively towards the lumen of the intestine (S. mansoni, S. japonicum) and bladder (S. haematobium) and are eliminated in the feces or urine, respectively. These eggs will hatch under ideal conditions, releasing miracidia, which penetrate specific snail (mollusk) intermediate hosts and develop into cercariae, continuing the life cycle. While many infections are asymptomatic, acute schistosomiasis (Katayama fever), due to S. mansoni or S. japonicum, may occur weeks after initial infection. Symptoms include fever, cough, abdominal pain, diarrhea, hepatosplenomegaly, and eosinophilia. Central nervous system infection is uncommon; however, cerebral granulomatous disease may be caused by migration of Schistosoma eggs into the brain or spinal cord. Cystitis and ureteritis with hematuria are associated with S. haematobium infection and can progress to bladder cancer. Diagnosis of schistosomiasis can be made by detection of eggs in fecal or urine samples as appropriate for each species. Antibody detection can be useful for patients who reside in nonendemic areas but have recently traveled to regions where Schistosoma species are found, and in whom eggs cannot be identified in fecal or urine examinations.

Useful For: Detection of antibodies to Schistosoma species

Interpretation: Negative: No IgG antibodies to Schistosoma species detected. Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive: IgG antibody to Schistosoma species detected. Differentiation between Schistosoma species is not possible by this assay. Serologic cross-reactivity may occur in individuals with other helminth infections, including with Echinococcus or Taenia species.

Reference Values:
Negative

Clinical References:

Scl 70 Antibodies, IgG, Serum

Clinical Information: Scl 70 (topoisomerase 1) is a 100-kD nuclear and nucleolar enzyme. Scl 70 antibodies are considered to be specific for scleroderma (systemic sclerosis) and are found in up to 60% of patients with this connective tissue disease. Scl 70 antibodies are more common in patients with extensive cutaneous involvement and interstitial pulmonary fibrosis, and are considered a poor prognostic sign. (1,2) See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients with signs and symptoms of scleroderma and other connective tissue diseases in whom the test for antinuclear antibodies is positive. Testing for Scl 70 antibodies are not useful in patients without demonstrable antinuclear antibodies.

Interpretation: A positive test result for Scl 70 antibodies is consistent with a diagnosis of scleroderma.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

FSCPR 75625

Scleroderma Comprehensive Profile

Clinical Information: Anti-U1 RNP Abs can be found in 2-14% of limited SSC and 5% of diffuse SSC. They are associated with isolated pulmonary arterial hypertension, arthritis and esophageal dysfunction. Anti-Th/To Abs are present in 2-6% of patients with limited SSC and are rarely found in diffuse SSC. They have specificity and are associated with isolated pulmonary arterial HTN, pulmonary fibrosis and renal crisis. Anti-U3 RNP (Fibrillarin) Abs are highly specific for diffuse SSC with a sensitivity of 4-10%. They are associated with isolated arterial hypertension, myositis, renal and cardiac manifestations of SSC. Anti-PM/SCL Abs are found in 25% of Scleroderma/myositis overlap, 10% of idiopathic inflammatory myopathy and 2% of Scleroderma cutaneous changes and ILD. Anti-RNA Polymerase III Abs are useful in the diagnosis of SSc and for the identification of patients at risk for developing renal crisis, progressive skin thickening and cancer. The prevalence of IgG RNAP III antibodies is 20-35% in diffuse SSC and 9% in limited SSC.

Reference Values:
Anti-Nuclear Ab by IFA, Anti-U3 RNP(Fibrillarin), Anti-Th/To Ab:
Reference Range: Negative

Anti-Centromere Ab:
Reference Range: <1:40

Anti-SCL-70 Ab:
Reference Range: <20

Anti-RNA Polymerase III, Anti-U1RNP Ab, and Anti-PM/Scl-100 Ab:
Reference Range: Negative:
<20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FSCN4 75263

SCN4A (Myotonia) DNA Sequencing Test

Reference Values:
A final report will be attached in MayoAccess.

SDHBZ 37442

SDHB Gene, Full Gene Analysis, Varies

Clinical Information: Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or...
sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted presymptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHB gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.
**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**SDHB Immunostain, Technical Component Only**

**Clinical Information:** Succinate dehydrogenase B (SDHB) protein is an integral part of the complex II oxidation/reduction pathway. Its function is to transfer electrons from succinate to CoQ. De novo and inheritable mutations in this gene result in paragangliomas and pheochromocytomas. SDHB can be used to differentiate between type 1 (SDHB +) and type 2 (SDHB -) gastrointestinal stromal tumors (GIST). SDHB-deficient GISTs do not respond to imatinib. The cellular localization for SDHB is cytoplasmic and staining is granular (localized to mitochondria). Endothelial cells often stain positive for SDHB and can be used as an internal control when testing GIST tumors.

**Useful For:** Aids in the identification of succinate dehydrogenase B (SDHB) deficient tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**SDHB, SDHC, SDHD Gene Panel, Varies**

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which...
gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDH shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited evidence about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason, there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with SDHB, SDHC, and SDHD gene mutations

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly
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**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**SDHCZ**

**SDHCZ 37443**

**SDHC Gene, Full Gene Analysis, Varies**

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHB variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHC, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains...
unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing:

(i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes:

SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHC gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
5. Benn DE, Richardson AL, Marsh DJ, Robinson BG: Genetic testing in pheochromocytoma and paraganglioma-associated syndromes. Ann NY Acad Sci 2006;1073:104-111
resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with new (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

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Seafood Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to seafood Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
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<td>0</td>
<td></td>
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<td>3.50-17.4</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.

**Seasonal Inhalants Allergen Profile, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to seasonal inhalants Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
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</tr>
</tbody>
</table>

**Reference values apply to all ages.**


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**Secobarbital, Serum**

**Clinical Information:** Secobarbital is a short-acting barbiturate with hypnotic properties used as a preanesthetic agent and in the short-term treatment of insomnia.(1,2) Secobarbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a volume of distribution of 1.6 to 1.9 L/kg, and about 46% to 70% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. The half-life of secobarbital is about 15 to 40 hours (mean: 28 hours).(2,3)

**Useful For:** Monitoring secobarbital therapy
**Interpretation:** Secobarbital concentrations above 5 mcg/mL have been associated with toxicity.

**Reference Values:**
- Therapeutic concentration: 1.0-2.0 mcg/mL
- Toxic concentration: >5.0 mcg/mL

**Clinical References:**

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**FSHP** 58038

**Sedative Hypnotic Panel, Urine-Forensic**

**Reference Values:**
The following threshold concentrations are used for this analysis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening Threshold</th>
<th>Confirmation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Alcohol</td>
<td>0.020 gm/dL</td>
<td>0.020 gm/dL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>300 ng/mL</td>
<td>100 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>100 ng/mL</td>
<td>75 ng/mL</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>100 ng/mL</td>
<td>300 ng/mL</td>
</tr>
</tbody>
</table>

Ketamine: Negative
- Screening threshold: 100 ng/mL

Gamma-Hydroxybutyric Acid (GHB): Negative
- Screening threshold: 5.0 ug/mL

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**SEWB** 65600

**Selenium, Blood**

**Clinical Information:** Selenium is a naturally occurring, solid substance that is widely but unevenly distributed in the earth's crust. Selenium and its compounds are used in some photographic devices, gun bluing, plastics, paints, anti-dandruff shampoos, vitamin and mineral supplements, fungicides, and certain types of glass. Selenium is also used to prepare drugs and as a nutritional feed supplement for poultry and livestock. It is an essential element for humans and animals. People are exposed to low levels of selenium daily through food, water, and air. Plasma and serum typically contain approximately 75% of the selenium measured in whole blood. Selenium whole blood concentrations can be used to assess tissue stores. For routine assessment of selenium deficiency or toxicity, the preferred test is selenium urine.

**Useful For:** Assessment of tissue stores of selenium

**Interpretation:** Ultimately, any metal ion concentration value needs to be interpreted in relation to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

**Reference Values:**
- 0-17 years: not established
- > or =18 years: 150-241 ng/mL

**Clinical References:**
2. Rifai N, Horvath AR, Wittwer CT; Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018
**Selenium, Serum**

**Clinical Information:** Selenium is an essential element. It is a cofactor required to maintain activity of glutathione peroxidase (GSH-Px), an enzyme that catalyzes the degradation of organic hydroperoxides. The absence of selenium correlates with loss of GSH-Px activity and is associated with damage to cell membranes due to accumulation of free radicals. The normal daily dietary intake of selenium is 0.01 to 0.04 parts per million (ppm), which is similar to the typical content of soil (0.05 ppm) and sea water (0.09 ppm). Selenium is found in many over-the-counter vitamin preparations because its antioxidant activity is thought to be anticarcinogenic. There is no supporting evidence that selenium suppresses cancer. In humans, cardiac muscle is the most susceptible to selenium deficiency. With cell membrane damage, normal cells are replaced by fibroblasts. This condition is known as cardiomyopathy and is characterized by an enlarged heart whose muscle is largely replaced by fibrous tissue. In the United States, selenium deficiency is related to use of total parenteral nutrition. This is therapy administered to patients with no functional bowel, such as after surgical removal of the small and large intestine because of cancer or because of acute inflammatory bowel disease such as Crohn disease. Selenium supplementation to raise the serum concentration to above 70 ng/mL is the usual treatment. Serum monitoring done on a semiannual basis checks the adequacy of supplementation. Selenium toxicity has been observed in animals when daily intake exceeds 4 ppm. Teratogenic effects are frequently noted in the offspring of animals living in regions where soil content is high in selenium such as south-central South Dakota and northern-coastal regions of California. Selenium toxicity in humans is not known to be a significant problem except in acute overdose cases. Selenium is not classified as a human teratogen.

**Useful For:** Monitoring selenium replacement therapy

**Interpretation:** Selenium accumulates in biological tissue. The normal concentration in adult human blood serum is 70 to 150 ng/mL (0.15 parts per million) with a population mean value of 98 ng/mL. Optimal selenium concentration is age dependent (see Reference Values); children require less circulating selenium than do adults. In the state of selenium deficiency associated with loss of glutathione peroxidase activity, the serum concentration is usually below 40 ng/mL.

**Reference Values:**
- 0-2 months: 45-90 ng/mL
- 3-6 months: 50-120 ng/mL
- 7-9 months: 60-120 ng/mL
- 10-12 months: 70-130 ng/mL
- >1 year: 70-150 ng/mL

**Clinical References:**

**Semen Analysis with Strict Morphology, Semen**

**Clinical Information:** Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm.
Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid. One of the more successful treatments for male and female infertility is in vitro fertilization (IVF). Male partners are tested with the strict criteria sperm morphology test prior to IVF to assist in the diagnosis of male-factor defects. Abnormalities in sperm morphology are related to: defects in sperm transport, sperm capacitation, the acrosome reaction, binding and penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple's IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).

**Useful For:** Determining male fertility status Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

**Interpretation:** Semen specimens can vary widely in the same man from specimen to specimen. semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient's fertility status. Sperm are categorized according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

**Reference Values:**

**SEMEN ANALYSIS**

- Appearance: normal
- Volume: > or =1.5 mL
- pH: > or =7.2
- Motile/mL: > or =6.0 x 10(6)
- Sperm/mL: > or =15.0 x 10(6)
- Motility: > or =40%
- Grade: > or =2.5

Note: Multiple laboratory studies have indicated that semen parameters for motility and grade on average retain 80% of original parameters when our shipping method is used for transport. Using these averages, samples with 32% to 39% motility and grade of 2 may be in the normal range if testing was performed shortly after collection. Therefore, these borderline patients may need to collect another sample at a local fertility center to verify fertility status

- Motile/ejaculate: > or =9.0 x 10(6)
- Viscosity: > or =3.0
- Agglutination: > or =3.0
- Supravital: > or =58% live
- Fructose: positive

Note: Fructose testing cannot be performed on semen analysis specimens shipped through Mayo Clinic Laboratories. If patient is azoospermic, refer to FROS / Fructose, Semen or Seminal Plasma. Submit separate specimen to rule-out ejaculatory duct blockage. Positive result indicates no blockage.

**STRICT MORPHOLOGY**

- Normal forms: > or =4.0% normal oval sperm heads
- Germ cells: <4 x 10(6) (normal)
- > or =4 x 10(6)/mL (elevated germinal cells in semen are of unknown clinical significance)
- WBC: <1 x 10(6) (normal)
- > or =1 x 10(6)/mL (elevated white blood cells in semen are of questionable clinical significance)

**Semen Analysis, Semen**

**Clinical Information:** Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid.

**Useful For:** Determining male fertility status

**Interpretation:** Semen specimens can vary widely in the same man from specimen to specimen. Semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient's fertility status.

**Reference Values:**
- Appearance: normal
- Volume: > or =1.5 mL
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**Seminal Fluid, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to seminal fluid. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>(&gt; \text{or} = 100)</td>
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</table>


**MIC 801659**

**Sensitivity, MIC (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**SEQA 113398**

**Sequential Maternal Screening, Part 1, Serum**

**Clinical Information:** Maternal serum screening is used to identify pregnancies that may have an increased risk for certain birth defects, such as trisomy 21 (Down syndrome), neural tube defects (NTD) and trisomy 18. Various options for maternal serum screening are available and include: first trimester, second trimester, and cross-trimester. Sequential screening is a type of cross-trimester screening which has an improved detection rate as compared to either first- or second-trimester screening. Sequential screening combines biochemical and ultrasound markers (nuchal translucency: NT) measured in both trimesters of the pregnancy. SEQA / Sequential Maternal Screening, Part 1, Serum involves an ultrasound and a blood draw. The ultrasound measurement, referred to as the NT measurement, is difficult to perform accurately. Therefore, NT data is accepted only from NT-certified sonographers. Along with the NT measurement, a maternal serum specimen is collected to measure pregnancy-associated plasma protein A (PAPP-A). The results of the ultrasound measurement and blood work, along with the maternal age and demographic information, are used to calculate Down syndrome and trisomy 18 risk estimates. If the result from part 1 indicates a risk for Down syndrome that is higher than the screen cutoff, the screen is completed and a report is issued. In that event, the patient is typically offered counseling and diagnostic testing. When the part 1 screen is completed, NTD risk is not provided. For a stand-alone NTD-risk assessment, order MAFP1 / Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum. If the risk from the first trimester is below the established cutoff, an additional serum specimen is collected in the second trimester for SEQB / Sequential Maternal Screen, Part 2, Serum. The blood sample is tested for AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A. The information from both trimesters is combined and a report is issued. If results are positive, the patient is typically offered counseling and diagnostic testing. NT: The NT measurement, an ultrasound marker, is obtained by measuring the fluid-filled space within the nuchal region (back of the neck) of the fetus. While fetal NT
measurements obtained by ultrasonography increase in normal pregnancies with advancing gestational age. Down syndrome and trisomy 18 fetuses have larger NT measurements than gestational age-matched normal fetuses. Increased fetal NT measurements can therefore serve as an indicator of an increased risk for Down syndrome and trisomy 18. PAPP-A: PAPP-A is a 187-kDA protein comprised of 4 subunits: 2 PAPP-A subunits and 2 pro-major basic protein (proMBP) subunits. PAPP-A is a metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4), dramatically reducing IGFBP-4 affinity for IGF1 and IGF2, thereby regulating the availability of these growth factors at the tissue level. PAPP-A is highly expressed in first-trimester trophoblasts, participating in regulation of fetal growth. Levels in maternal serum increase throughout pregnancy. Low PAPP-A levels before the fourteenth week of gestation are associated with an increased risk for Down syndrome and trisomy 18.

**Useful For:** First-trimester prenatal screening for Down syndrome (trisomy 21) and trisomy 18

**Interpretation:** Maternal screens provide an estimation of risk, not a diagnosis. A negative result indicates that the estimated risk falls below the screen cutoff. A positive result indicates that the estimated risk exceeds the screen cutoff. Down Syndrome (trisomy 21): First-trimester results are negative when the calculated risk is below 1/50 (2%). If part 1 is negative, submit an additional specimen in the second trimester (order SEQB / Sequential Maternal Screening, Part 2, Serum). Second-trimester results are negative when the calculated risk is below 1/270 (0.37%). Negative results mean that the risk is less than the established cutoff; they do not guarantee the absence of Down syndrome. Results are positive when the risk is greater than the established cutoff (ie, > or =1/50 in the first trimester and > or =1/270 in the second trimester). Positive results are not diagnostic. When both sequential maternal screening parts 1 and 2 are performed with a screen cutoff of 1/270, the combination of maternal age, nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 90% with a false-positive rate of approximately 3% to 4%. In practice, both the detection rate and false-positive rate vary with maternal age. Trisomy 18: In part 1, trisomy 18 results are only reported if the Down syndrome risk is positive. In part 2, the screen cutoff for trisomy 18 is 1/100 (1%). Risks that are greater or equal to 1% are screen-positive; positive results are not diagnostic. Risks less than 1% are screen-negative; negative results do not guarantee the absence of trisomy 18. Use caution when revising trisomy 18 positive results with earlier dating. Babies with trisomy 18 tend to be small, which can lead to underestimation of gestational age and an increased chance of missing a true-positive. When sequential maternal screening parts 1 and 2 are performed, the overall detection rate is approximately 90% with a false-positive rate of approximately 0.1% using a screen cutoff of 1/100. Neural Tube Defect: Risk assessment for neural tube defects (NTD) is only available after completion of part 2 of the sequential maternal screen. See SEQB / Sequential Maternal Screening, Part 2, Serum for details. Follow-up: Verify that all information used in the risk calculation is correct (maternal date of birth, gestational dating, etc). If any information is erroneous, contact the laboratory for a revision. Screen-negative results typically do not warrant further evaluation. If the results are positive, the patient is typically offered counseling, ultrasound, diagnostic testing, and possibly, referral to genetics counseling or a high-risk clinic.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Sequential Maternal Screening, Part 2, Serum**

**Clinical Information:** Maternal serum screening is used to identify pregnancies that may have an increased risk for certain birth defects, such as trisomy 21 (Down syndrome), neural tube defect (NTD) and trisomy 18. Various options for maternal serum screening are available and include: first trimester, second trimester, and cross-trimester. Sequential screening is a type of cross-trimester screening, which has an improved detection rate as compared to either first- or second-trimester screening. Sequential screening combines biochemical and ultrasound markers (nuchal translucency: NT) measured in both trimesters of the pregnancy. SEQA / Sequential Maternal Screening, Part 1, Serum involves an ultrasound and a blood collection. The ultrasound measurement, referred to as the NT measurement, is difficult to perform accurately. Therefore, NT data is accepted only from NT-certified sonographers. Along with the NT measurement, a maternal serum specimen is collected to measure pregnancy-associated plasma protein A (PAPP-A). The results of the ultrasound measurement and blood work along with the maternal age and demographic information are used to calculate Down syndrome and trisomy 18 risk estimates. If the result from part 1 indicates a risk for Down syndrome that is higher than the screen cutoff, the screen is completed and a report is issued. In that event, the patient is typically offered counseling and diagnostic testing. When the part 1 screen is completed, a NTD risk is not provided. For a stand-alone NTD-risk assessment, order MAFP1 / Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum. If the risk from the first trimester is below the established cutoff, an additional serum specimen is collected in the second trimester for SEQB / Sequential Maternal Screening, Part 2, Serum. The blood sample is tested for AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A. The information from both trimesters is combined and a report is issued. If results are positive, the patient is typically offered counseling and diagnostic testing. Alpha-Fetoprotein (AFP): AFP is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from a nonpregnancy level of 0.2 to about 250 ng/mL at 32 weeks gestation. If the fetus has an open NTD, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal-distress situations such as threatened abortion and fetal demise, may also show AFP elevations. Additionally, increased maternal serum AFP values may be seen in pregnancies with multiple fetuses and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP values have been associated with an increased risk for genetic conditions such as Down syndrome and trisomy 18. Unconjugated Estriol (uE3): Estriol, the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the intact feto-placental unit. Estriol exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of uE3 in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates estriol to make it more water soluble for urinary excretion. Estriol levels increase during the course of pregnancy. Decreased uE3 has been shown to be a marker for Down syndrome and trisomy 18. Low levels of estriol also have been associated with pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Human Chorionic Gonadotropin (hCG): hCG is a glycoprotein consisting of 2 noncovalently-bound subunits. The alpha subunit is identical to the alpha subunits of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. The CGA gene (glycoprotein hormones, alpha polypeptide) is thought to have developed through gene duplication from the LH gene in a limited number of mammalian species. hCG only plays an important physiological role in primates (including humans), where it is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum, and hence progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total beta hCG levels are associated with Down syndrome, while decreased levels may be seen in trisomy 18. Elevations of hCG also can be seen in pregnancies with multiple fetuses, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetalis. Inhibin A:
Inhibins are a family of heterodimeric glycoproteins, primarily secreted by ovarian granulosa cells and testicular Sertoli cells, which consist of disulfide-linked alpha and beta subunits. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta A or a beta B chain, they are designated as inhibin A or inhibin B, respectively. Together with the related activins, which are homodimers or heterodimers of beta A and B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the feto-placental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibin A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibin A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibin A levels are typically higher in Down syndrome pregnancies). However, despite their similar behavior, measuring maternal serum inhibin A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for Down syndrome.

Useful For: Prenatal screening for Down syndrome, neural tube defects, and trisomy 18 Identifying abnormal levels of alpha-fetoprotein in the second trimester

Interpretation: Maternal screens provide an estimation of risk, not a diagnosis. A negative result indicates that the estimated risk falls below the screen cutoff. A positive result indicates that the estimated risk exceeds the screen cutoff. Neural Tube Defect: Screen-negative results indicate that the alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the screen cutoff of 2.50 MoM. A negative screen does not guarantee the absence of a neural tube defect (NTD). A screen-positive result indicates that the calculated AFP MoM is greater or equal to 2.50 MoM and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual's pretest risk of having a child with a NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with open NTDs have AFP MoM values of greater than 2.50. Down Syndrome: Second-trimester results are negative when the calculated risk is below 1/270 (0.37%). Negative results mean that the risk is less than the established cutoff; they do not guarantee the absence of Down syndrome. Results are positive when the risk is greater than the established cutoff (> or =1/270). Positive results are not diagnostic. When both sequential maternal screening parts 1 and 2 are performed with a screen cutoff of 1/270, the combination of maternal age, nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 90% with a false-positive rate of approximately 3% to 4%. In practice, both the detection rate and false-positive rate vary with maternal age. Trisomy 18: The screen cutoff for trisomy 18 is 1/100 (1%) in the second trimester. Risks that are greater or equal to 1% are screen-positive; positive results are not diagnostic. Risks less than 1% are screen-negative; negative results do not guarantee the absence of trisomy 18. Use caution when revising trisomy 18 positive results with earlier dating. Babies with trisomy 18 tend to be small, which can lead to underestimation of gestational age and an increased risk of missing a true-positive. When sequential maternal screening parts 1 and 2 are performed the overall detection rate is approximately 90% with a false-positive rate of approximately 0.1% using a screen cutoff of 1/100. Follow-up: Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (maternal date of birth, gestational dating, etc). If any information is incorrect, the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. If the results are positive, the patient is typically offered counseling, ultrasound, diagnostic testing, and, possibly, a referral to genetics counseling or a high-risk clinic.

Reference Values: An interpretive report will be provided.

SALS

Serologic Agglut Method 1 Ident (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

EC

Serologic Agglut Method 2 Ident (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

SIDC

Serologic Agglut Method 4 Ident (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FSERO

SeroNeg RAdx3 Profile

Clinical Information: SeroNeg RAdx3 is a diagnostic and prognostic panel for Rheumatoid Arthritis designed to complement traditional RF and Anti-CCP testing. This profile, consisting of 14-3-3 eta protein, Anti -CEP-1 Ab and Anti-Sa Ab, enhances the diagnosis of established or early RA (in individuals seronegative for RF and Anti-CCP Ab) and also helps predict disease severity. Decrease in 14-3-3eta and/or Anti-Sa Ab with treatment is associated with less radiographic progression. The presence of Anti-CEP1 and Anti-CCP Antibodies suggests the imminent progression of pre-clinical RA into clinical RA

Reference Values:
Interpretation for:
14.3.3 ETA, Rheum. Arthritis:
Reference Range: <0.20 ng/mL
Negative: A Â Â Â Â Â Â Â Â Â Â Â Â Â Â Â <0.20 ng/mL
Weak Positive: A Â Â Â Â Â 0.20-0.39 ng/mL
Moderate Positive: 0.40-0.79 ng/mL
Strong Positive: Â Â Â >0.79 ng/mL

Interpretation for:
Anti-CEP-1 Ab, IgG and Anti-Sa Ab, IgG:
Reference Range: <20
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units
Serotonin Release Assay, Unfractionated Heparin

Reference Values:

<table>
<thead>
<tr>
<th>UFH SRA Result</th>
<th>% release</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH Low Dose, 0.1 IU/mL</td>
<td>% release</td>
</tr>
<tr>
<td>UFH Low Dose, 0.5 IU/mL</td>
<td>% release</td>
</tr>
<tr>
<td>UFH High Dose, 100 IU/mL</td>
<td>% release</td>
</tr>
</tbody>
</table>

A sample is considered negative if there is: <20% release.

An interpretive comment included with results.

Serotonin, 24 Hour, Urine

Clinical Information: Serotonin (5-hydroxytryptamine) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HTP). Serotonin production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral serotonin pools are isolated from each other. EC-cell production accounts for 80% of the body’s serotonin content. Many different stimuli can release serotonin from EC-cells. Once secreted, in concert with other gut hormones, serotonin increases GI blood flow, motility, and fluid secretion. On first pass through the liver 30% to 80% of serotonin is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in serotonin are neuroectodermal tumors, in particular tumors arising from EC-cells, which are termed carcinoid. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). The enzyme 5-HTP decarboxylase, which converts the intermediate 5-HTP to serotonin, is present in midgut tumors, but is absent or present in low concentrations in foregut and hindgut tumors. Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly serotonin, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by serotonin. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of serotonin. Because midgut tumors drain into the portal circulation, which passes into the liver, undergoing extensive hepatic (first-pass) serotonin degradation, symptoms do not usually occur until liver or other distant metastases have developed, producing serotonin that bypasses the hepatic degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urine serotonin, urine 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells. Urine serotonin is, in most circumstances, the least likely marker to
be elevated (see Interpretation).

**Useful For:** The diagnosis of a small subgroup of carcinoid tumors that produce predominately 5-hydroxytryptophan (5-HP), but very little serotonin and chromogranin A. Follow-up of patients with known or treated carcinoid tumors that produce predominately 5-HP, but very little serotonin and chromogranin A.

**Interpretation:** It is usually impossible to diagnose asymptomatic, small carcinoid tumors by measurement of serum or urine serotonin, urine 5-hydroxyindoleacetic acid (5-HIAA), or serum chromogranin A. By contrast, 1 or more of these markers are elevated in most patients with more advanced and symptomatic tumors, usually to levels several times the upper limit of the reference interval. In patients with advanced and symptomatic tumors the following patterns of tumor marker elevations are observed: - Serum or whole blood serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors, because foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HP) decarboxylase activity and, therefore, may produce little, if any, serotonin. - Urine 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. - Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. - Urine serotonin is in most circumstances the least likely marker to be elevated. The exception is tumors (usually foregut tumors) that produce predominately 5-HP, rather than serotonin, and also secrete little, if any, chromogranin A. In this case, circulating chromogranin A, circulating serotonin levels, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HP to serotonin, leading to high urine serotonin levels. Urine serotonin measurements are not commonly employed in carcinoid tumor follow-up. The exceptions are patients with tumors that almost exclusively secrete 5-HP, as summarized above. In these individuals, urine serotonin is the tumor marker of choice to monitor disease progression. In all other patients, disease progression is monitored best using urinary 5-HIAA and serum chromogranin A measurements. These markers are usually proportional to the patient’s tumor burden over a wide range of tumor extent and tumor secretory activity.

**Reference Values:**

< or =210 mcg/24 hours

Reference values apply to all ages.

**Clinical References:**

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**Serotonin, Blood**

**Clinical Information:** Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content. Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver, 30% to 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further
platelet aggregation. The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular, tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

**Useful For:** In conjunction with, or as an alternative to first-order test in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-HIAA or serum chromogranin A measurements are first-line tests) Second-order test in the follow-up of patients with known or treated carcinoid tumors in whole blood specimens

**Interpretation:** Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations greater than 1,000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HTP, rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to 5-HT, leading to high urinary 5-HT levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html


Serotonin, Serum

Clinical Information: Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HTP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content. Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver 30% to 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far less 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

Useful For: In conjunction with, or as an alternative to first-order test in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-HIAA or serum chromogranin A measurements are first-line tests) Second-order test in the follow-up of patients with known or treated carcinoid tumors in serum specimens

Interpretation: Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations greater than 1,000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser
increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5 hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HTP, rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to 5-HT, leading to high urinary 5-HT levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

Reference Values:
< or =230 ng/mL


SERPZ

SERPINA1 Gene, Full Gene Analysis, Varies

Clinical Information: Alpha-1-antitrypsin (A1A) is a protein that inhibits the enzyme neutrophil elastase. It is predominantly synthesized in the liver and secreted into the bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema, which initially affects the lung bases (as opposed to smoking-related emphysema, which presents with upper lung field emphysema). Patients may become symptomatic in their 30s and 40s. The most frequent symptoms reported in a National Institute of Health study of 1,129 patients with severe deficiency (mean age 46 years) included cough (42%), wheezing (65%), and dyspnea with exertion (84%). Many patients were misdiagnosed as having asthma. It is estimated that approximately one-sixth of all lung transplants are for A1A deficiency. Liver disease can also occur, particularly in children; it occurs much less commonly than emphysema in adults. A1A deficiency is a relatively common disorder in Northern European Caucasians. The diagnosis of A1A deficiency is initially made by quantitation of protein levels in serum followed by phenotyping-determination of specific allelic variants by isoelectric focusing (IEF), genotyping-DNA based detection of specific mutations, or proteotyping-using liquid chromatography-tandem mass spectrometry (LC-MS/MS). While there are many different alleles in this gene, only 3 are common. The 3 major alleles include: M (full functioning, normal allele), S (associated with reduced levels of protein), and Z (disease-causing mutation associated with liver disease and premature emphysema). The S and Z alleles account for the majority of the
abnormal alleles detected in affected patients. As a codominant disorder, both alleles are expressed. An individual of SZ or S- null genotype may have a small increased risk for emphysema (but not liver disease) due to slightly reduced protein levels. On the other hand, an individual with the ZZ genotype is at greater risk for early onset liver disease and premature emphysema. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. Historically, IEF phenotyping has been the primary method for characterizing variants, though in some cases the interpretation is difficult and prone to error. Serum quantitation is helpful in establishing a diagnosis but can be influenced by other factors. IEF phenotyping, LC-MS/MS proteotyping, and DNA-based genotyping are routinely used to test for deficiency alleles, but can miss disease alleles other than the S and Z alleles. In patients suspected to have alpha-1 antitrypsin deficiency based on clinical findings or serum alpha-1-antitrypsin (AAT) levels, who do not have evidence of the SZ or ZZ genotype by routine methods, this gene analysis assay may provide useful information. Full sequencing of the SERPINA1 coding region is performed for the detection of rare non-S or non-Z disease mutations. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

Useful For: Identification of causative mutations when a deficient serum level of alpha-1-antitrypsin is not explained by routine testing, such as proteotyping, genotyping, or isoelectric focusing phenotyping. Determining the specific allelic variant (full gene analysis) for prognosis and genetic counseling

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

FSERT 91345
Sertraline (Zoloft) and Desmethylsertraline

Reference Values:
Sertraline:
Reference Range: 30 - 200 ng/mL
Report Limit 10 ng/mL

Desmethylsertraline: ng/mL
No reference range provided

The stated reference range is the range of observed steady-state concentrations in individuals receiving therapeutic dosage regimens of sertraline. This is not a defined therapeutic range.
Report Limit 10 ng/mL

SESA 82728
Sesame Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to sesame seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or ≥100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) IgG, Blood Spot**

**Clinical Information:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. The incubation period for COVID-19 ranges from 2 to 14 days. Typically, immunocompetent individuals with COVID-19 develop detectable SARS-CoV-2 IgG-class antibodies 8 to 14 days following onset of symptoms. Patients tested prior to this time may be negative for SARS-CoV-2 IgG antibodies.

**Useful For:** Screening for the detection of IgG-class antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using dried blood spot specimens This test should not be used to detect recent or acute coronavirus disease 2019 (COVID-19) or for documentation of SARS-CoV-2
vaccine response.

**Interpretation:** Negative: No IgG antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detected. Negative results may occur if the test is done too soon following infection, in patients who are immunosuppressed, or in patients with very mild or asymptomatic infection. This test does not rule out active or recent coronavirus disease 2019 (COVID-19) and will not detect SARS-CoV-2 vaccine-induced antibodies. Positive: Results suggest infection with SARS-CoV-2 at some time in the past. A positive result does not indicate protection against reinfection with SARS-CoV-2. False-positive results may occur. Confirmatory testing using a venipuncture blood draw may be considered in low-risk individuals or those residing in low-prevalence regions. Inconclusive: Presence or absence of antibodies to SARS-CoV-2 could not be determined. Repeat testing on a new dried blood spot specimen or a venipuncture blood draw may be considered.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**
hospitalization or death), failures of serologic and/or molecular diagnostic assays, and significant reduction in neutralization by antibodies generated from previous infection or vaccination, and reduced efficacy of monoclonal antibody therapy or vaccines. Current SARS-CoV-2 variants of interest in the US are the B.1.1.7, B.1.351, B.1.427, B.1.429, and P.1 lineages. A SARS-CoV-2 variant of high consequence has clear evidence of significantly reduced effectiveness of current preventive measures, therapeutic agents, and medical interventions, when compared to previously circulating variants. At present, there are no such variants in US or globally.

**Useful For:** Distinguishing between persistent infection with the same viral strain and re-infection with a new viral strain in an individual with recurrent positive molecular test results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Detection and identification of vaccine-escape SARS-CoV-2 variants with spike (S) gene variant of interest Detection and identification of SARS-CoV-2 variants containing S gene variants of interest that reduce the efficacy of vaccine-induced antibodies, convalescent plasma, and/or monoclonal antibody therapy for COVID-19

**Interpretation:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific S gene mutations are detected with this assay at a minimum 50% frequency for detecting codon substitutions in the viral sequence. An "Inconclusive" result indicates that testing failed due to poor sequence quality resulting from the presence of inhibitory substances and/or low amount of virus (ie, PCR target cycle threshold [Ct] value of >30.0) present in the submitted specimen. A new specimen should be collected and submitted for retesting if clinically necessary. The table below indicates the clinical implications of known SARS-CoV-2 variants of interest and variants of concern: SARS-CoV-2 PANGO lineage

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Efficacy of convalescent plasma therapy</th>
<th>Efficacy of monoclonal antibodies</th>
<th>Efficacy of Pfizer/BioNTech mRNA vaccine</th>
<th>Efficacy of Moderna mRNA vaccine</th>
<th>Efficacy of J and J adenovirus vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7</td>
<td>No effect</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>B.1.351</td>
<td>Unknown</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>B.1.427</td>
<td>Unknown</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>B.1.429</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>B.1.525</td>
<td>Unknown</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>B.1.617</td>
<td>Unknown</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>S codon mutation of interest</th>
<th>Effect on viral transmission and infectivity</th>
<th>Effect on severity of disease</th>
<th>Efficacy of vaccines</th>
<th>Efficacy of monoclonal antibodies</th>
<th>Efficacy of vaccines</th>
<th>Efficacy of monoclonal antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>H69-V70 deletion**</td>
<td>Unknown</td>
<td>Increased</td>
<td>Unknown</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Y144 or Y145 deletion</td>
<td>Unknown</td>
<td>Increased</td>
<td>Unknown</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>

**Notes:** a. Based on in vitro (experimental) data only. b. Reduced efficacy of bamlanivimab, etesevimab, and casirivimab. c. Reduced efficacy of bamlanivimab and etesevimab. d. Reduced efficacy of bamlanivimab and casirivimab. The table below indicates the clinical implications of known codon-substitutions in the SARS-CoV-2 spike protein (S) encoding region: S codon mutation of interest Effect on viral transmission and infectivity Effect on severity of disease Efficacy of convalescent plasma therapy Efficacy of monoclonal antibodies* Efficacy of vaccines

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*Based on in vitro (experimental) data only.

**This dual codon mutation also causes failure of certain molecular detection assays.
Reference Values:
Not applicable


Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA and Influenza Virus Type A and Type B RNA Detection, PCR, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2. Influenza, also known as the "flu," is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management.


Interpretation: A "Detected" result indicates that the specific virus is present and suggests infection with the virus. Test results should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that the specific virus is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, quality, and type of the specimen collected for testing. Result should be correlated with patientâ€™s history and clinical presentation. An "Indeterminate" result suggests that the patient may be infected with a variant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or SARS-related coronavirus. Additional testing with an alternative molecular method is recommended on a newly collection specimen may be considered if the patient does not have signs and/or
symptoms of coronavirus disease 2019 (COVID-19). An "Inconclusive" result indicates that the presence or absence of the specific virus in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to reverse transcription-polymerase chain reaction (RT-PCR) inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected


Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Detection, PCR, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2.

Useful For: Detection of coronavirus disease 2019 (COVID-19) illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Recommended only for patients who meet current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives: www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html

Interpretation: A "Detected" result indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is present and suggests the diagnosis of coronavirus disease 2019 (COVID-19). Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, quality, and type of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Indeterminate" result suggests that the patient may be infected with a variant SARS-CoV-2 or SARS-related coronavirus. Additional testing with an alternative molecular method may be considered if the patient does not have signs or symptoms of COVID-19. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to RT-PCR inhibition. Submission of a new specimen for testing is recommended. Sequence analyses have predicted that this assay will detect the circulating variants reported by the U.S. Centers for Disease Control and Prevention (www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html), such as the United Kingdom (B.1.1.7), South Africa (B.1.351), and Brazil (P.1) variants.
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Detection, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms may be nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2.

Useful For: Diagnosis of coronavirus disease 2019 (COVID-19) illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Recommended only for patients who meet current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives.

Interpretation: Based on sequence analysis, this assay is predicted to detect the circulating variants reported by the U.S. Centers for Disease Control and Prevention (www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html), such as the United Kingdom (B.1.1.7), South Africa (B.1.351), and Brazil (P.1) variants. A "Detected" result indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is present and suggests the diagnosis of coronavirus disease 2019 (COVID-19). Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. A summary of available treatment options for COVID-19 can be found at the U.S. Department of Health and Human Services website: https://combatcovid.hhs.gov/i-have-covid-19-now/available-covid-19-treatment-options An "Undetected" result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, as well as the quality and type of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Indeterminate" result suggests that the patient may be infected with a variant SARS-CoV-2 or SARS-related coronavirus. Additional testing with an alternative molecular method may be considered if the patient does not have signs and/or symptoms of COVID-19. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to RT-PCR inhibition. Submission of a new specimen for testing is recommended.

Reference Values: Undetected

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Detection, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms may be nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2.

Useful For: Diagnosis of coronavirus disease 2019 (COVID-19) illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Recommended only for patients who meet current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives

Interpretation: A "Detected" result indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is present and suggests the diagnosis of coronavirus disease 2019 (COVID-19). Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, as well as the quality and type of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to real-time reverse transcription polymerase chain reaction (RT-PCR) inhibition. Submission of a new specimen for testing is recommended.

Reference Values: Undetected

**Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA, Varies**

**Clinical Information:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms maybe nonspecific and resemble other common respiratory infections, such as influenza. If testing for other respiratory infections is negative, specific testing for SARS-CoV-2 (COVID-19) may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2.

**Useful For:** Diagnosis of coronavirus disease 2019 (COVID-19) illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Recommended only for patients who meet current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives: www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html

**Interpretation:** A Detected result indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is present and suggests the diagnosis of coronavirus disease 2019 (COVID-19). Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An Undetected result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, quality and type of specimen collected for testing. Result should be correlated with patient’s history and clinical presentation. An Inconclusive result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to RT-PCR inhibition. Submission of a new specimen for testing is recommended.

**Reference Values:** Undetected

**Clinical References:**

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**Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Nucleocapsid, Total Antibody, Serum**

**Clinical Information:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronavirus. All coronaviruses share similarities in the organization and expression of their genome, which encodes 16 nonstructural proteins and the 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). Results are for the detection of SARS-CoV-2 antibodies. Antibodies to SARS-CoV-2 are generally detectable in blood several days after initial infection; although the duration of time antibodies are present postinfection is not well characterized. Patients may have detectable virus present...
for several weeks following seroconversion.

**Useful For:** Aiding in identifying individuals with an adaptive immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), indicating recent or prior infection

**Interpretation:** Negative: No antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detected. Negative results may occur in serum collected too soon following infection, in patients who are immunosuppressed, or in patients with mild or asymptomatic infection. This test does not rule out active or recent coronavirus disease 2019 (COVID-19) and will not detect SARS-CoV-2 vaccine-induced antibodies. Follow-up testing with a molecular test is recommended in symptomatic patients. Positive: SARS-CoV-2 antibodies to the nucleocapsid protein detected. Results suggest recent or prior infection with SARS-CoV-2. Correlation with epidemiologic risk factors and other clinical and laboratory findings is recommended. Serologic results should not be used to diagnose recent SARS-CoV-2 infection. Protective immunity cannot be inferred based on these results alone. False-positive results may occur due to cross-reactivity from pre-existing antibodies or other possible causes.

**Reference Values:**

**Clinical References:**

**RSARB 613979**

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Rapid, PCR Charge (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**SCOVT 610689**

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), RNA Detection, ddPCR, Tissue

**Clinical Information:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point, lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid, transbronchial biopsy, wedge biopsy of lung, autopsy lung specimen) would be more likely to have detectable
SARS-CoV-2. Infection of other tissue has been reported. The SARS-CoV-2 RNA detection in formalin-fixed and paraffin-embedded (FFPE) tissue by droplet digital polymerase chain reaction (ddPCR) assay will be used to detect the nucleocapsid N1 and N2 target sequences of SARS-CoV-2 virus in FFPE surgical and autopsy tissue. The identification of SARS-CoV-2 in surgical tissue may aid in the diagnosis of COVID-19 and may lead to a better understanding of unusual disease presentations. Detection of SARS-CoV-2 in deceased patients (autopsy tissue) may similarly confirm a suspected diagnosis among individuals with clinical or pathologic manifestations of COVID-19 (ie, pulmonary, cardiac) and may increase understanding of SARS-CoV-2 pathobiology.

**Useful For:** Detection of severe respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) in formalin-fixed, paraffin-embedded tissue

**Interpretation:** This test will be reported as positive, negative, or indeterminate. An "indeterminate" result indicates that the presence or absence of severe respiratory syndrome coronavirus 2 (SARS-CoV-2 RNA) in the specimen could not be determined with certainty after repeated testing in the laboratory. This could be due to reverse transcriptase polymerase chain reaction (RT-PCR) inhibition or very low viral load. Submission of a new specimen for testing is recommended. Test results should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis.

**Reference Values:**
Not applicable

**Clinical References:**
disease 2019 (COVID-19) infection or vaccination. Follow up testing with a molecular test for SARS-CoV-2 is recommended in symptomatic patients. Positive: Antibodies to the SARS-CoV-2 spike glycoprotein detected. These results suggest recent or prior SARS-CoV-2 infection or vaccination. No minimum antibody level or threshold has been established to indicate long-term protective immunity against re-infection. Correlation with epidemiologic risk factors and other clinical and laboratory findings is recommended. Serologic results should not be used to diagnose recent SARS-CoV-2 infection. False-positive results for IgG antibodies may occur due to cross-reactivity from pre-existing antibodies or other possible causes. For the manufacture of COVID-19 convalescent plasma using the Roche Diagnostics anti-SARS-CoV-2 spike electro-chemiluminescence immunoassays (ECLIA), per current FDA Emergency Use Authorization (EUA) guidelines, high-titer cyclic citrullinated peptide (CCP) is defined as plasma units with a semi-quantitative value of 132 U/mL and above (see appendix A: www.fda.gov/media/141477/download).

**Reference Values:**
Negative

**Clinical References:**

**SCDGP 62190**

**Severe Combined Immunodeficiency Panel (63 genes), Next-Generation Sequencing, Varies**

**Clinical Information:** Severe combined immunodeficiency (SCID) is characterized by the absence or dysfunction of T lymphocytes, which affects both cellular and humoral adaptive immunity resulting in a severe form of this inherited primary immunodeficiency disorder (PIDD) that may be life-threatening. In classic form, SCID presents in infancy with persistent respiratory and gastrointestinal infections, failure to thrive, or graft-versus-host disease (due to engraftment of maternal T cells). The absence of lymphoid tissue, immunoglobulins, and T lymphocytes may also be noted. Typically, patients will have less than 300 autologous CD3 T cells/mcL blood and will require immediate medical intervention. Atypical or "leaky" SCID tends to present later (ie, over 12 months of age) with recurrent, severe, and prolonged viral infections, bronchiectasis, autoimmune manifestations including cytopenias, and failure to thrive. Patients may display partial or restricted antigen-specific antibody responses. Leaky SCID is also related to hypomorphic variants in genes normally associated with classic SCID, as indicated above. Omenn syndrome, a form of leaky SCID that typically presents in infancy, is characterized by erythroderma, alopecia, hepatosplenomegaly, and lymphadenopathy. Laboratory findings may include elevated IgE, eosinophilia, and lymphocytosis. Omenn syndrome is due to genetic variants in at least 7 different genes that allow for partial activity, although disease severity is likely only partially attributable to genotype. While RAG1 and RAG2 hypomorphic variants are most often associated with leaky SCID or Omenn syndrome, patients may have variants affecting other genes/proteins, such as Artemis or Interleukin-7 receptor (IL-7R) alpha. There may be forms of leaky SCID with hypomorphic variants in these genes that do not have the associated Omenn syndrome phenotype. SCID can be classified as T-B+ or T-B- SCID, with further subdivision possible based on
the presence or absence of NK cells. T-B+ SCID, characterized by impaired development of mature T-cells along with present but non-functional B-cells, is most often caused by genetic variants that affect cytokine-mediated signaling. X-linked SCID is due to mutations in the IL2RG gene, which encodes the common gamma chain that is a part of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. Autosomal recessive forms due to variants in JAK3 or IL7R also disrupt cytokine signaling. Genetic variants in one of the four CD3 genes (CD3G, CD3D, CD3E, and CD247[CD3Z]) inhibit CD3 signaling and also cause T-B+ SCID. T-B+ SCID may also be due to corin-1A deficiency causing disruption of thymic egress of T cells and defective T cell locomotion, or due to CD45 deficiency (caused by variants in PTPRC). Patients with corin-1A deficiency may also have other syndromic manifestations. T-B-SCID is typically characterized by a defect in V(D)J recombination. V(D)J recombination begins with proteins encoded by RAG1 and RAG2 forming a heterodimer and making a single-stranded nick and forming hairpin structured ends between a coding element (V, D, or J segment) and the recombination signal sequence. Then, in the processing phase, the DNA-protein kinase complex (including a protein encoded by PRKDC) binds to and opens the hairpin structure by phosphorylating Artemis (encoded by DCLRE1C). Prior to ligation of the open ends by LIG4/XRCC4 and Cernunnos/XLF (encoded by NHEJ1), additional editing takes place. Adenosine deaminase (ADA) deficiency, which results in accumulation of metabolic by-products that are toxic to lymphocytes, and results in T-B- and NK-SCID. It accounts for approximately 15% of cases and is inherited as an autosomal recessive condition, which may include neurological problems (ie, cognitive impairment, hearing/visual impairment, and movement disorders) in addition to SCID. Reticular dysgenesis, due to genetic variants in AK2, is the most severe form of combined immunodeficiency and is characterized by congenital agranulocytosis, lymphopenia, lymphoid and thymic hypoplasia, along with bilateral sensorineural deafness. Subsets of T cells may be decreased due to genetic variants in certain genes, without an appreciable effect on other T cell subsets. For example, genetic variants in CD8A, ZAP70, TAP1, TAP2, or TAPBP can result in absent or reduced CD8+ T cells in the presence of normal quantity of CD4+ T cells. In contrast, genetic variants in CIITA, RFXANK, RFX5, or RFXAP result in absent or reduced CD4+ T cells. These genes are associated with bare lymphocyte syndromes types 1 and 2 respectively, or major histocompatibility complex (MHC) class I and II deficiencies. In addition, variants in ITK, MAGT1, RHOH, STK4, TRAC, LCK, MALT1, IL21, IL21R, TNFRSR4 (OX40), IKBKB, CD27, or CTPS1 are thought to generally result in combined immunodeficiency that is generally less clinically profound than SCID. Several combined immunodeficiencies are associated other features and syndromes. Variants in WAS and WIFP1 present with combined immunodeficiency and congenital thrombocytopения, while variants in RBM8A are associated with thrombocytopenia-absent radius (TAR) syndrome. DNA repair defects are commonly observed along with combined immunodeficiency in ataxia-telangiectasia (due to variants in ATM). Thymic defects with additional congenital anomalies may be observed in DiGeorge syndrome (represented on this panel by TBX1), CHARGE syndrome (due to variants in CHD7 or SEMA3E), and patients with genetic variants in FOXN1. Immune-osseous dysplasias along with combined immunodeficiency may be observed in cartilage hair hypoplasia (due to variants in RMRP), while those with variants in STAT5B may have growth hormone insensitivity. Combined immunodeficiency (CID) along with defects of vitamin B12 and folate metabolism may be observed in patients with genetic variants in SLC46A1 or MTHFD1. Anhidrotic ectodermal dysplasia with immunodeficiency results from genetic variants in IKBK (NEMO) or NFKBIA (IKBA). Calcium channel defects are an associated feature in those with variants in ORAI1 or STIM1. In addition to CID, patients with variants in TTC7A may have multiple intestinal atresias. Barth syndrome along with combined immunodeficiency can be observed in patients with variants in TAZ. Some of these defects can be identified by newborn screening (NBS) for SCID, while others do not present with severe enough T cell lymphopenia in the neonatal period to be identified by NBS. Table 1. Genes included in the Severe Combined Immunodeficiency (SCID)/Combined Immunodeficiency (CID)/T-cell Lymphopenia/Deficiency/Bare Lymphocyte Syndrome (BLS)/EBV-associated Primary Immunodeficiency Gene Panel GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER ADA (ADA1) Adenosine deaminase 608958 1-9 per million live births AR, partial ADA deficiency may lead to delayed or milder presentation SCID (T-, Ig-, NK-) ADA2 (CECR1) Adenosine deaminase CECR1 isoform a precursor 607575 1-9 per million live births AR SCID (T-, Ig-, NK-) Sneddon syndrome, polyarteritis nodosa, childhood-onset, early-onset stroke, vasculopathy, B cell immunodeficiency, neutrophil and macrophage polarization defects AK2 Adenylate kinase 2, mitochondrial isoform a 103020 AR SCID (T-, Ig-, normal, Ig- with granulocytopenia, deafness), reticular dysgenesis ATM Serine-protein kinase ATM 607585 1/40,000-100,000 AR Ataxia-telangiectasia and combined immunodeficiency (T with abnormal
proliferation to mitogens, B+, Ig often decreased [particularly IgA, IgE, and IgG with increased IgM monomers]) CD247 (CD3Z) T-cell surface glycoprotein CD3 zeta chain isoform 1 precursor 186780 AR SCID (T+B normal), Ig- NK normal, no gamma/delta T cells CD27 CD27 antigen precursor 186711 AR Combined immunodeficiency (T+B no memory, Ig hypogamma-globulinemia following EBV), lymphoproliferative syndrome 2 CD3D T-cell surface glycoprotein CD3 delta chain isoform A precursor 186790 AR SCID (T+B-, Ig-, NK+, no gamma/delta T cells) CD3E T-cell surface glycoprotein CD3 epsilon chain isoform 1 precursor 186830 AR SCID (T+B-, Ig-, NK+, no gamma/delta T cells) CD3G T-cell surface glycoprotein CD3 gamma chain isoform 1 precursor 186740 AR Combined immunodeficiency (T-normal with reduced TCR expression, B+ Ig+) CD8A T-cell surface glycoprotein CD8 alpha chain isoform 1 precursor 186910 AR CD8 deficiency (normal CD4 cells, B+, Ig+) CHD7 Chromodomains-helicase-DNA-activated protein 7 isoform 1 608892 AD Combined immunodeficiency (T decreased/normal [response to PHA may be decreased], B+, Ig decreased/normal), CHARGE syndrome CIITA MHC class II transactivator isoform 2 600005 AR Combined immunodeficiency (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig decreased/normal) CORO1A Coronin-1A 605000 AR SCID (T-B+, Ig-, with detectable thymus EBV-associated B-cell lymphoproliferation), CGD CTPO1 CTPO synthase 1 isoform a 123860 AR Combined immunodeficiency (T decreased/normal with decreased/normal proliferation, B decreased/normal, Ig high/normal) DCLRE1C (ARTEMIS) Protein Artemis isoform a 609588 1/2,000 in Athabaskan-speaking populations AR SCID (T-B-, Ig- with radiation sensitivity), omenn syndrome FOXN1 Forkhead box protein N1 600838 AR Combined immunodeficiency (T markedly decreased, B+, Ig decreased) congenital alopecia, and nail dystrophy, nude SCID GATA2 Endothelial transcription factor GATA-2 isoform 1 137295 AD Immunodeficiency with multilineage cytopenias, omenn syndrome, susceptibility to acute myeloid leukemia and myelodysplastic syndrome 1 IL7R IL7R 146661 AR SCID (T- B+, Ig decreased/normal with decreased CD4 lymphopenia, low Treg, restricted T repertoire and impaired TCR signaling; B normal, Ig decreased) IL21 Interleukin-21 605383 AR/AD Immunodeficiency (abnormal T cell cytokine production and abnormal proliferation to specific stimuli, B normal, Ig normal but impaired specific responses), elevated IgE (autosomal dominant) IL2RG Cytokine receptor common subunit gamma precursor 308380 Approximately 1/50,000-100,000 live births XL SCID (T-, B+(normal to increased), Ig-, NK-) IL7R IL7R 146661 AR SCID (T-B+, Ig decreased, NK+), omenn syndrome ITK Tyrosine-protein kinase ITK/TSK 186973 Rare AR Immunodeficiency (progressive T cell disease with normal B cells and normal/decreased Ig), lymphoproliferative syndrome 1, EBV susceptibility JAK3 Tyrosine-protein kinase JAK3 600173 Rare AR Combined immunodeficiency (T normal total numbers but low function, B low, IgG deficiency), severe early onset colitis IL21R Interleukin-21 receptor isoform 1 precursor 1 605383 AR/AD Immunodeficiency (abnormal T cell cytokine production and abnormal proliferation to specific stimuli, B normal, Ig normal but impaired specific responses), elevated IgE (autosomal dominant) IKBKG (NEMO) NF-kappa-B essential modulator isoform a 300248 Rare XL Combined immunodeficiency (T decreased/normal with poor activation, B normal [low memory B cells], Ig decreased with poor specific antibody responses), anhidrotic ectodermal dysplasia, mycobacterial susceptibility IL21 Interleukin-21 605384 AR Immunodeficiency (T normal number but low function, B low, IgG deficiency), severe early onset colitis IL21R Interleukin-21 receptor isoform 1 precursor 1 605383 AR/AD Immunodeficiency (abnormal T cell cytokine production and abnormal proliferation to specific stimuli, B normal, Ig normal but impaired specific responses), elevated IgE (autosomal dominant) IL2RG Cytokine receptor common subunit gamma precursor 308380 Approximately 1/50,000-100,000 live births XL SCID (T-, B+(normal to increased), Ig-, NK-) IL7R IL7R 146661 AR SCID (T-B+, Ig decreased, NK+), omenn syndrome ITK Tyrosine-protein kinase ITK/TSK 186973 Rare AR Immunodeficiency (progressive T cell disease with normal B cells and normal/decreased Ig), lymphoproliferative syndrome 1, EBV susceptibility JAK3 Tyrosine-protein kinase JAK3 600173 1/500,000 live births AR SCID (T-B+, Ig-, NK-) LCK Tyrosine-protein kinase LCK 153390 AR Combined immunodeficiency (T normal total numbers but CD4 lymphopenia, low Treg, restricted T repertoire and impaired TCR signaling; B normal, Ig decreased) IL21 Interleukin-21 605383 AR/AD Immunodeficiency (abnormal T cell cytokine production and abnormal proliferation to specific stimuli, B normal, Ig normal but impaired specific responses), elevated IgE (autosomal dominant) IL2RG Cytokine receptor common subunit gamma precursor 308380 Approximately 1/50,000-100,000 live births XL SCID (T-, B+(normal to increased), Ig-, NK-) IL7R IL7R 146661 AR SCID (T-B+, Ig decreased, NK+), omenn syndrome ITK Tyrosine-protein kinase ITK/TSK 186973 Rare AR Immunodeficiency (progressive T cell disease with normal B cells and normal/decreased Ig), lymphoproliferative syndrome 1, EBV susceptibility JAK3 Tyrosine-protein kinase JAK3 600173 1/500,000 live births AR SCID (T-B+, Ig-, NK-) LCK Tyrosine-protein kinase LCK 153390 AR Combined immunodeficiency (T normal total numbers but CD4 lymphopenia, low Treg, restricted T repertoire and impaired TCR signaling; B normal, Ig decreased)
substrate 2 602049 AD (in progress) Neutrophil immunodeficiency syndrome; identified with T cell lymphopenia in NBS SCID; may affect T cell numbers and/or function RAG1 V(D)J recombination-activating protein 1 179615 Approximately 1/100,000 live births AR SCID (T-B-, Ig-, NK+), omenn syndrome RAG2 V(D)J recombination-activating protein 2 179616 Approximately 1/100,000 live births AR SCID (T-B-, Ig-, NK+), omenn syndrome RBM8A RNA-binding protein 8A 605313 AR Thrombocytopenia-absent radius syndrome RFX5 DNA-binding protein RFX5 601863 AR Bare lymphocyte syndrome (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig+/decreased) RFXANK DNA-binding protein RFXANK isoform a 603200 AR Bare lymphocyte syndrome (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig+/decreased) RFXAP Regulatory factor X-associated protein 1 601861 AR Bare lymphocyte syndrome (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig+/decreased) RHOH Rho-related GTP-binding protein RhoH precursor 602037 AR Combined immunodeficiency (T normal but low naive T cells, restricted repertoire, and impaired proliferation in response to CD3; B+, Ig+) RMRP RNA component of mitochondrial RNA processing endoribonuclease 157660 AR Cartilage-hair hypoplasia, SCID (T severely decreased to normal with impaired proliferation; B_, Ig normal or reduced); Omenn syndrome SEMA3E Semaphorin-3E isoform 1 precursor 608166 AD CHARGE syndrome; Combined immunodeficiency (T decreased/normal [response to PHA may be decreased], B+, Ig decreased/normal) SH2D1A SH2 domain-containing protein 1A isoform 1 300490 1/million males XL X-linked lymphoproliferative syndrome (normal/increased activated T cells, reduced memory B cells, partially defective NK cell and CTL cytotoxic activity) SLCA46A1 Proton-coupled folate transporter isoform 1 611672 AR Combined immunodeficiency related to folate deficiency (T variable, B variable, Ig decreased); megaloblastic anemia STAT5B Signal transducer and activator of transcription 5B 604260 Rare AR Immunodeficiency (T modestly decreased, B+, Ig+) with growth hormone insensitivity STIM1 Stromal interaction molecule 1 isoform 1 205921 AR/AD Immunodeficiency (T normal with defective TCR mediated activation, B+, Ig+)(AR) STK4 SERINE/THREONINE PROTEIN KINASE 4 614868 AR Combined immunodeficiency (T: altered proportion of terminal differentiated effector memory cells with restricted repertoire, low naive T cells, impaired proliferation; B decreased, Ig high) TAP1 Antigen peptide transporter 1 isoform 1 170260 AR Bare lymphocyte syndrome (decreased CD8 with absent MHC I expression on lymphocytes, normal B cells, normal Ig) with vasculitis TAP2 Antigen peptide transporter 2 isoform 2 170261 AR Bare lymphocyte syndrome (decreased CD8 with absent MHC I expression on lymphocytes, normal B cells, normal Ig) with vasculitis TAPBP Tapasin isoform 1 precursor 601962 AR Bare lymphocyte syndrome (decreased CD8 with absent MHC I expression on lymphocytes, normal B cells, normal Ig) with vasculitis TAZ Tafazzin isoform 1 603927 XL Barth syndrome TBX1 T-box transcription factor TBX1 isoform C 602054 AD DiGeorge syndrome with immunodeficiency (T decreased or normal, B normal, Ig normal or decreased) TNFRSF4 (OX40) Tumor necrosis factor receptor superfamily member 4 precursor 600315 AR Immunodeficiency (normal T cell numbers with decreased antigen specific memory CD4; normal B cell numbers with reduced memory B cells; normal Ig) TRAC T cell receptor alpha constant 186880 AR Immunodeficiency (TCR-alpha/beta deficiency and impaired T cell proliferation; B+, Ig+) TTC7A Tetratricopeptide repeat protein 7A isoform 2 609332 AR Immunodeficiency with multiple intestinal atresias (T variable/ absent, B+, Ig decreased) WAS Wiskott-Aldrich syndrome protein 300392 XL, GOF Wiskott-Aldrich syndrome (progressive disease with abnormal lymphocyte responses to anti-CD3, B+, Ig decreased) WAS/WASL-interacting protein family member 1 602357 AR Wiskott-Aldrich syndrome (reduced/defective lymphocyte responses to anti-CD3; B low; Ig normal except increased IgE) XIAP (BIRC4) E3 ubiquitin-protein ligase XIAP 300079 1/million males XL X-linked lymphoproliferative syndrome (increased T cell susceptibility to apoptosis to CD95 and enhanced activation-induced cell death) ZAP70 Tyrosine-protein kinase ZAP-70 isoform 1 176947 AR Selective ADA=adenosine deaminase AD=autosomal dominant AR=autosomal recessive GOF=gain of function MHC=major histocompatibility complex XL=X-linked

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of severe combined immunodeficiency (SCID), combined immunodeficiency (CID), T-cell lymphopenia/deficiency, bare lymphocyte syndrome (BLS), or Epstein-Barr virus-associated primary immunodeficiency disorder (PIDD) Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying pathogenic variants within genes known to be associated SCID, CID, T-cell lymphopenia/deficiency, BLS, or EBV-associated PIDD allowing for predictive testing of at-risk family members

Current as of June 14, 2021 12:13 pm CDT  800-533-1710 or 507-266-5700 or mayocliniclabs.com  Page 2296
**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.


### Sex Chromosome Determination, FISH, Tissue

**Clinical Information:** Genotypically normal females possess 2 X chromosomes (XX); genotypically normal males possess 1 X chromosome and 1 Y chromosome (XY). Determining the sex chromosome complement in a tissue specimen can be used to: -Identify opposite sex-donor cells post-transplant -Help resolve cases of suspected sample mix-up

**Useful For:** Identifying the sex chromosome complement in paraffin-embedded tissues

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

Sex Hormone-Binding Globulin, Serum

Clinical Information: Sex hormone-binding globulin (SHBG), a 95 KDa homodimer, is the blood transport protein for testosterone and estradiol. SHBG is mainly produced in the liver and has a half-life of approximately seven days. SHBG binds reversibly to sex steroids. SHBG has a relatively high binding affinity to dihydrotestosterone (DHT), medium affinity to testosterone and estradiol, and exhibits a low affinity to estrone, dehydroepiandrosterone (DHEA), androstenedione, and estriol. Albumin, which exists at physiologically higher concentrations than SHBG, also binds to sex steroids although with a much lower binding affinity (eg, about 100 times lower for testosterone). Decreased SHBG serum concentrations are associated with conditions in which elevated androgen concentrations are present or the effect of androgen on its target organs is excessive. Because of the high binding affinity of SHBG to DHT, as compared to estradiol, SHBG has profound effects on the balance between bioavailable androgens and estrogens. Increased SHBG concentrations may be associated with symptoms and signs of hypogonadism in men, while decreased concentrations can result in androgenization in women. SHBG is also regulated by insulin, and a low SHBG concentration often indicates insulin resistance and, consequently, may be a predictor of type 2 diabetes. Endogenous or exogenous thyroid hormones or estrogens increase SHBG concentrations. In men, there is also an age-related gradual rise, possibly secondary to the mild age-related fall in testosterone production. This process can result in bioavailable testosterone concentrations that are much lower than would be expected based on total testosterone measurements alone.

Useful For: Diagnosis and follow-up of women with symptoms or signs of androgen excess (eg, polycystic ovarian syndrome and idiopathic hirsutism) An adjunct in monitoring sex-steroid and antiandrogen therapy An adjunct in the diagnosis of disorders of puberty An adjunct in the diagnosis and follow-up of anorexia nervosa An adjunct in the diagnosis of thyrotoxicosis (tissue marker of thyroid hormone excess) A possible adjunct in diagnosis and follow-up of insulin resistance and cardiovascular and type 2 diabetes risk assessment, particularly in women

Interpretation: Many conditions of mild-to-moderate androgen excess in women, particularly polycystic ovarian syndrome, are associated with low sex hormone-binding globulin (SHBG) concentrations. A defect in SHBG production could lead to bioavailable androgen excess, in turn causing insulin resistance that depresses SHBG concentrations further. There are rare cases of SHBG variants that follow this pattern. SHBG concentrations are typically very low in these individuals. However, in most patients, SHBG concentrations are mildly depressed or even within the lower part of the reference interval. In these patients, the primary problem may be androgen overproduction, insulin resistance, or both. Adult SHBG concentrations in adolescent males with signs of precocious puberty support that the condition is testosterone driven, rather than representing premature adrenarche. Therapies/behavior alterations that potentially increase SHBG concentrations include reducers of bioactivity of androgens (eg, androgen receptor antagonists, alpha-reductase inhibitors) or reduction of insulin resistance (eg, weight loss, metformin, peroxisome proliferator-activated receptor [PPAR] gamma agonists). Clinical assays may not be available for many therapeutic synthetic androgens and estrogens (eg, ethinyl-estradiol). In those instances, increasing SHBG concentrations may be associated with anti-androgen or estrogen therapy, while SHBG reduction can be associated with androgen treatment. Patients with anorexia nervosa have high SHBG concentrations. With successful treatment, concentrations start to fall as nutritional status improves. Normalization of SHBG precedes, and may be predictive of, future normalization of reproductive function. Thyrotoxicosis increases SHBG concentrations. In situations when assessment of true functional thyroid status may be difficult (eg, patients receiving amiodarone treatment, individuals with thyroid hormone transport-protein abnormalities, patients with suspected thyroid hormone resistance or suspected inappropriate thyroid-stimulating hormone [TSH] secretion such as a TSH-secreting pituitary adenoma), elevated SHBG concentrations suggests tissue thyrotoxicosis, while a normal level indicates euthyroidism or near-euthyroidism. SHBG is also produced by placental tissue and therefore values will be elevated during pregnancy. Reference ranges for pregnant females have not been established in our institution. In patients with known insulin resistance, “metabolic syndrome,” or high risk of type 2 diabetes (eg, women with a history of gestational diabetes), low SHBG concentrations may predict...
progressive insulin resistance, cardiovascular complications, and progression to type 2 diabetes. An increase in SHBG concentrations may indicate successful therapeutic intervention. A genetic variant of SHBG (Asp327>Asn) introduces an additional glycosylation site in 10% to 20% of the population, resulting in significantly slower degradation. These individuals tend to have higher SHBG concentrations for any given level of other factors influencing SHBG. In laboratories without access to bioavailable testosterone or equilibrium dialysis-based "true" free testosterone assays, sex hormone-binding globulin measurement is crucial in cases when assessment of the free testosterone fraction (free androgen index or calculated free testosterone) is required. At Mayo Clinic Laboratories, both bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) and free testosterone (TGRP / Testosterone, Total and Free, Serum) measurements are available. Free testosterone (TGRP) is measured by equilibrium dialysis, obviating the need for sex hormone-binding globulin measurements to calculate free androgen fractions.

Reference Values:

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<th>Reference Interval (nmol/L)</th>
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<td>Stage V</td>
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<table>
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<th>Tanner Stages</th>
<th>Mean Age</th>
<th>Reference Interval (nmol/L)</th>
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<tbody>
<tr>
<td>Stage I</td>
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<td>Stage II</td>
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<td>7.7-108</td>
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<tr>
<td>Stage V</td>
<td>14.9</td>
<td>10-79 ADULTS Â Â Â Â Â Â Â Males &gt; or =18 years: 13.3-89.5 nmol/L Females 18-46 years: 18.2-135.5 nmol/L 47-91 years, post-menopausal: 16.8-125.2 nmol/L</td>
</tr>
</tbody>
</table>

Clinical Information: This test is appropriate for individuals with a 46,XX karyotype and phenotypically normal male external genitalia, a 46,XY karyotype and phenotypically normal female external genitalia, clinical features suggestive of 46,XX testicular disorder of sex development with normal male external genitalia, and clinical features suggestive of 46,XY complete gonadal dysgenesis. The SRY (sex-determining region on the Y chromosome) gene is required for normal embryonic wolffian (male) genital development, although numerous other genes are involved in completing the process of normal male development. Some gene mutations block the action of SRY in development. Thus, a 46,XY individual with an SRY deletion or mutation will develop as a female, and a 46,XX individual with translocation of SRY to 1 X chromosome will develop as a male. Structural abnormalities of the Y chromosome result in a spectrum of abnormalities from primary infertility (male or female) to various forms of ambiguous genitalia. SRY-negative 46,XX males often have ambiguous genitalia, whereas those who are positive for SRY usually have a normal male phenotype with azoospermia. SRY-negative 46,XY females may have another mutation, such as 1 involving the SOX9 gene. We recommend conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood) to detect Y chromosome abnormalities and to rule out other chromosome abnormalities or translocations, and FISH studies to detect cryptic translocations involving the SRY region that are not demonstrated by conventional chromosome studies.

Useful For: Detecting the deletion or addition of the SRY gene in conjunction with conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood)

Interpretation: Any male individual with an SRY signal on a structurally normal Y chromosome is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe. Any patient with a FISH signal on an X chromosome will be reported as having a cryptic X;Y translocation involving the critical region.

Reference Values: An interpretive report will be provided.


Sezary Diagnostic Flow Cytometry, Blood

Clinical Information: Sezary syndrome is a leukemic form of cutaneous T-cell lymphoma (CTCL). By definition, it is associated with systemic skin involvement (erythroderma) and the presence of at least 1000/mcL of circulating cells with irregular nuclear features (Sezary cells). Morphologic assessment of the number of Sezary cells has been proven to have low reproducibility. Therefore, WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors adopted alternative methods to assess circulating T-cells in order to establish the diagnosis of Sezary syndrome. These include CD4:CD8 ratio of more than 10:1, and selective loss of CD7 and/or CD26 on 40% and 30% of the CD4-positive cell population, respectively. It is important to recognize that the later criteria (fulfilled by peripheral blood flow cytometry immunophenotyping) are relative, and not in direct correlation with absolute counts of Sezary cells defined by morphology.

Useful For: Identifying phenotypically aberrant T-cell population in peripheral blood as part of the diagnostic workup for Sezary syndrome Roughly assessing the circulating tumor burden in mycosis fungoides, if the phenotype of the neoplastic cells is distinctive enough

Interpretation: Sezary cells typically show loss of CD7 and/or CD26. As loss of these markers is not completely sensitive or specific for Sezary cells, and there are circulating normal CD4-positive T-cells, which usually cannot be excluded from the analysis, the WHO/European Organization for Research and
Treatment of Cancer (EORTC) classification of skin tumors proposed cutoffs of 30% for CD26 loss and 40% for CD7 loss on CD4-positive T-cells as diagnostic criteria for Sezary syndrome. In addition, a CD4:CD8 ratio of greater than or equal to 10:1 in a gated T-cell population is also considered abnormal and part of the diagnostic algorithm for Sezary syndrome. In mycosis fungoides staging studies the cutoffs are even less clearly defined. The clinical outcome was worse in patients with more than 5% of circulating lymphocytes showing Sezary-like morphology. However, flow cytometry immunophenotyping is deemed useful for relative quantification of these cells only if they can be separated by aberrant expression of other surface markers. In the majority of cases, this cannot be accomplished to the proposed cutoff point (5% of circulating lymphocytes). The test will be resulted as “No phenotypically aberrant T-cell population detected” if there is no specific phenotype that allows separation of potentially abnormal CD4-positive T-cells, loss of CD26 (and/or CD7) is present in less than 30% (40%), and CD4:CD8 ratio is less than 10:1. If any of the above aberrancies are present, the test will be resulted as “Phenotypically distinct T-cell population is detected” with a description of phenotype, percentage of total CD4-positive population, and percentage of total analyzed events. In addition, the phenotype will be compared to that of any distinct T-cell population previously seen in the same patient by our laboratory.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

Clinical References:

Sezary Monitoring Flow Cytometry, Blood

Clinical Information: Sezary syndrome is a leukemic form of cutaneous T-cell lymphoma (CTCL). By definition, it is associated with systemic skin involvement (erythroderma) and the presence of at least 1000/mcL of circulating cells with irregular nuclear features (Sezary cells). Morphologic assessment of the number of Sezary cells has been proven to have low reproducibility. Therefore, WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors adopted alternative methods to assess circulating T-cells in order to establish the diagnosis of Sezary syndrome. These include CD4:CD8 ratio of more than 10:1, and selective loss of CD7 and/or CD26 on 40% and 30% of the CD4-positive T-cell population, respectively. It is important to recognize that the later criteria (fulfilled by peripheral blood flow cytometry immunophenotyping) are relative, and not in direct correlation with absolute counts of Sezary cells defined by morphology.

Useful For: Monitoring response to therapy in patients with previously diagnosed Sezary syndrome or mycosis fungoides

Interpretation: Sezary cells typically show loss of CD7 and/or CD26. As loss of these markers is not completely sensitive or specific for Sezary cells, the WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors proposed cutoffs of 30% for CD26 loss and 40% for CD7 loss on CD4-positive T-cells, as diagnostic criteria for Sezary syndrome. In addition, CD4:CD8 ratio of greater than or equal to 10:1 in a gated T-cell population is also considered abnormal, and part of diagnostic algorithm for Sezary syndrome. In mycosis fungoides staging studies the cutoffs
are even less clearly defined. The clinical outcome was worse in patients with more than 5% of circulating lymphocytes showing Sezary-like morphology. However, flow cytometry immunophenotyping is deemed useful for relative quantification of these cells only if they can be separated by aberrant expression of other surface markers. In majority of cases, this cannot be accomplished to the proposed cutoff point (5% of circulating lymphocytes). The test will be resulted as "No phenotypically aberrant T-cell population detected" if there is no specific phenotype that allows separation of potentially abnormal CD4-positive T-cells, loss of CD26 (and/or CD7) is present in less than 30% (40%), and CD4:CD8 ratio is less than 10:1. If any of the above aberrancies are present, the test will be resulted as "Phenotypically distinct T-cell population is detected" with a description of phenotype, percentage of total CD4-positive population and percentage of total analyzed events. In addition, the phenotype will be compared to that of any distinct T-cell population previously seen in the same patient by our laboratory.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.


SF1 Immunostain, Technical Component Only

Clinical Information: Steroidogenic factor 1 (SF-1) is a transcription factor involved in the development of the anterior pituitary and is useful in the classification of pituitary adenomas. Expression of SF-1 is observed in gonadotropin hormone producing tumors (follicular stimulating or luteinizing hormone).

Useful For: Classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values: Not applicable

**Sheep Wool, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to sheep wool Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Shiga Toxin, Molecular Detection, PCR, Feces**

**Clinical Information:** Shiga toxins (also known as Shiga-like toxins, Vero toxins, or Vero-like toxins) are encoded by some strains of Escherichia coli, most notably O157:H7. Shiga toxin can also be produced by other serogroups of enterohemorrhagic E coli (EHEC), as well as Shigella dysenteriae type 1. Generally, Shiga toxin-producing organisms cause bloody diarrhea, although this is not universal. Unlike some bacterial gastrointestinal infections, antimicrobial therapy is contraindicated, as antimicrobials may exacerbate disease. Treatment is primarily supportive (eg, hydration). A complication of infection by an organism producing Shiga toxin is hemolytic uremic syndrome (HUS). The percentage of people that develop HUS varies among outbreaks of E coli O157:H7, but generally
ranges from 3% to 20%. HUS is characterized by a triad of findings: hemolytic anemia, thrombocytopenia, and kidney failure. Most people recover completely, however, some require permanent dialysis, and some die as a result of complications. Several diagnostic methods that are available for the detection of EHEC lack sensitivity, are labor intensive, or have a long turnaround time. There are more than 160 serogroups of EHEC; the first serogroup to be associated with HUS was O157:H7. This is also the serogroup that is most commonly implicated in outbreaks. EHEC O157:H7 is detectable as non-fermenting colonies when cultured on sorbitol MacConkey (SMAC) agar, but the majority of non-O157:H7 Shiga toxin-producing E. coli strains ferment sorbitol and, therefore, are undetectable by this method. The Vero cell line is susceptible to the Shiga toxin, but the assay can take up to 48 hours and is nonspecific. Commercial enzyme-linked immunosorbent assay (ELISA) antigen detection kits have a sensitivity of 90% when compared to culture, but an overnight enrichment step is necessary for adequate sensitivity. PCR detection of stx, the gene encoding Shiga toxin, directly from fecal specimens is a sensitive and specific technique, providing same-day results. PCR assay identifies non-O157:H7 Shiga toxin-producing bacteria, extending the utility beyond strains identifiable on SMAC agar.

**Useful For:** Sensitive, specific, and rapid detection of the presence of Shiga toxin-producing organisms such as Escherichia coli O157:H7 and Shigella dysenteriae type 1 in stool. This test is not recommended as a test of cure.

**Interpretation:** A positive polymerase chain reaction (PCR) result indicates the likely presence of Shiga toxin-producing Escherichia coli in the specimen. Although Shigella dysenteriae serotype 1 may produce a positive result, it is extremely rare in the United States. A negative result indicates the absence of detectable Shiga toxin DNA in the specimen, but does not rule out the presence of Shiga toxin-producing E. coli and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Shiga toxin DNA in quantities less than the limit of detection of the assay. Shiga toxins are encoded on mobile genetic elements and can theoretically be lost by their bacterial host.

**Reference Values:**
Not applicable

**Clinical References:**

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**Shigella Culture, Feces**

**Clinical Information:** Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Shigella species are common causative agents of bacterial diarrheal disease worldwide. The infectious dose is low; Shigella transmission can occur via contaminated food and water or from direct person-to-person contact.

**Useful For:** Determining whether Shigella species may be the cause of diarrhea. Reflexive testing for Shigella species from nucleic acid amplification test-positive stool. This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.
Interpretation: The growth of Shigella species identifies a potential cause of diarrhea.

Reference Values:
No growth of pathogen

Clinical References:

Short Ragweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to short ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Clinical References: Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry’s Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
SCADZ 35544

Short-Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency, Full Gene Analysis, Varies

Clinical Information: Short-chain acyl-CoA dehydrogenase (SCAD) catalyzes the first step in the mitochondrial beta-oxidation of fatty acids with a chain length of 6 to 4 carbons. SCAD deficiency is a rare autosomal recessive condition. The clinical phenotype of SCAD shows considerable variability and is incompletely defined. Of those reported cases, hypoglycemia, developmental delay, and muscle hypotonia are the most common indicated features. The diagnosis of SCAD deficiency is challenging and should be based on the clinical presentation, 2 or more findings of ethylmalonic aciduria, and determination of fatty acid flux in fibroblasts indicating deficient SCAD activity. Molecular genetic analysis of the gene associated with SCAD (ACADS) may confirm the biochemical phenotype of SCAD deficiency. The first step in evaluation for SCAD deficiency is identification of 2 or more findings of ethylmalonic aciduria, as determined by either OAU / Organic Acids Screen, Urine or ACYLG / Acylglycines, Quantitative, Urine. Ethylmalonic aciduria is a common, although not specific, laboratory finding in patients with SCAD deficiency. Determination of fatty acid flux in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) is warranted for an individual with 2 or more findings of ethylmalonic aciduria. DNA sequencing of the ACADS gene is typically utilized only when SCAD deficiency is identified through biochemical analysis. The ACADS gene, associated with SCAD deficiency, is located on chromosome 12q22 and consists of 10 exons. Molecular genetic studies revealed that some patients carry ACADS gene mutations that cause complete absence of SCAD activity, while others carry ACADS gene variants (511C->T;625G->A) that may confer disease susceptibility only in association with other factors. The allele frequencies in the general population of the 511C->T and 625G->A gene variants are 3% and 22%, respectively. The presence of 2 of these gene variants is not considered an independent diagnostic marker for SCAD deficiency. Although further investigation is needed, it is most likely that these variants are not clinically significant. Identification of 2 ACADS gene mutations that cause complete absence of SCAD activity alone is not sufficient to explain or determine possible clinical phenotype or prognosis. The clinical significance of carrying 2 mutations is often uncertain. Therefore, the results of ACADS gene sequencing for SCAD deficiency should be interpreted in light of the clinical presentation and biochemical findings in each case.

Useful For: Preferred molecular analysis to confirm a diagnosis of short-chain acyl-CoA dehydrogenase deficiency (as a follow-up to the biochemical analyses only)

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


FSHDH 75677

SHOX, DHPLC

Useful For: Identifies mutations causing short stature related to SHOX deficiency. SHOX deficiency is...
an indication for somatotropin (Humatrope®).

**Reference Values:**
An interpretive report will be provided.

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**FSHRG 57542**

**Shrimp IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**SHRI 82677**

**Shrimp, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to shrimp Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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### Sickle Solubility, Blood

**Clinical Information:** Homozygous hemoglobin (Hb) S (sickle cell disease) is a serious chronic hemolytic anemia most commonly found in those of African or Middle Eastern descent. Hb S is freely soluble when fully oxygenated; when oxygen is removed, polymerization of the abnormal hemoglobin occurs, forming tactoids that are rigid and deformed cells. This leads to sickling of the cells, hemolysis, and many other complications. Heterozygous Hb S (sickle cell trait) is the most common hemoglobinopathy in the United States. This condition is present in about 8% of African Americans. Usually, Hb S trait exhibits no clinical or hematological effects. A small fraction of people with sickle cell trait have recurrent hematuria.

**Useful For:** Screening for presence or absence of hemoglobin (Hb) S (sickle cell disease)

**Interpretation:** A positive result should be followed by a complete hemoglobin (Hb) evaluation (HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood) to confirm the presence and concentration of Hb S.

**Reference Values:**
Negative


### STAT6

**Clinical Information:** Signal transducer and activator of transcription 6 (STAT6) is a signal transducer/transcription activator expressed in the cytoplasm of various normal tissues including bladder epithelium, bronchial epithelium, and epidermis. NAB2-STAT6 fusions have recently been described in the majority of solitary fibrous tumors (SFT), and lead to aberrant strong nuclear STAT6 staining.

**Useful For:** Aids in distinguishing solitary fibrous tumor from morphologic mimics

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


### Silicon, Serum

**Interpretation:** Specimens for elemental testing should be collected in certified metal-free containers. Elevated results for elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen.

**Reference Values:**

- Reporting limit determined each analysis.
- Generally: Less than 0.05 mg/dL
- Silicon concentrations are influenced by diet, especially vegetable intake.

### Silk, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to silk

- Defining the allergen responsible for eliciting signs and symptoms
- Identifying allergens: responsible for allergic disease and/or anaphylactic episode
- Confirm sensitization prior to beginning immunotherapy
- Investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
**Silver Birch, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to silver birch Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**Sinemet, Serum**

**Interpretation:** Levodopa The target plasma concentration of levodopa in Parkinsonian patients is 2 +/- 0.5 mcg/mL. The average peak plasma levodopa concentration following a single oral dose of Sinemet containing 200 mg levodopa was 1.2 mcg/mL at 0.5 hours for normal release and 3.3 mcg/mL at 2 hours for controlled release. At steady-state, the average trough plasma levodopa concentration following oral Sinemet containing 200 mg levodopa was 0.07 mcg/mL for normal release and 0.16 mcg/mL for controlled release. Carbidopa Following a single oral dose of 250 mg levodopa and 25 mg carbidopa, peak plasma concentrations of carbidopa averaged 0.11 mcg/mL at 2.9 hours post dose. Carbidopa concentrations can decrease rapidly after collection unless flash frozen with dry ice.
Reference Values:
Reporting limit determined each analysis.

Levodopa
Å Units: mcg/mL

Carbidopa
Å Units: mcg/mL

Sirolimus, Whole Blood
Clinical Information: Sirolimus is a macrolide antibiotic, isolated from Streptomyces hygroscopicus, with potent effects including suppression of T- and B-cell proliferation and antineoplastic and antifungal activity. It inhibits the protein kinase mTOR to arrest the cell cycle; it has no effects on calcineurin and, therefore, can be used in addition to cyclosporine or tacrolimus, or as a substitute in patients intolerant to these drugs. Sirolimus is metabolized by CYP3A4, thus, blood concentrations are affected by drugs that inhibit or induce this enzyme. The pharmacokinetic interaction between sirolimus and cyclosporine or tacrolimus increases both therapeutic immunosuppression and the toxicity of these agents; lower doses are required with combined use. Adverse effects of sirolimus are generally concentration dependent, making therapeutic drug monitoring essential. Trough sirolimus concentrations are generally measured every 5 days. Target concentrations vary depending on concomitant therapy, time posttransplant, the desired degree of immunosuppression, and adverse effects. When given with cyclosporine or tacrolimus, the therapeutic range for sirolimus is generally between 4 and 12 ng/mL with minimal added benefit for concentrations >10 ng/mL. When sirolimus is given without calcineurin inhibitors, higher trough levels are needed; usually 12 to 20 ng/mL, but occasionally up to 20 to 30 ng/mL.

Useful For: Monitoring whole blood sirolimus concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to sirolimus with trough whole blood levels 4 to 20 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comediations. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before a scheduled dose). Blood drawn at other times will yield higher results. The assay is specific for sirolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, tacrolimus, tacrolimus metabolites, or sirolimus metabolites. Results by liquid chromatography with detection by liquid chromatography-tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
4-20 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Sm Antibodies, IgG, Serum

Clinical Information: Sm (Smith) is a small nuclear ribonucleoprotein composed of several protein autoantigens designated B, B1, D, E, F, and G, which range in size from 11 kD to 26 kD. Sm antibodies are specific for lupus erythematosus (LE) and occur in approximately 30% of LE patients. The levels of Sm antibodies remain relatively constant over time in patients with LE and are usually found in patients that also have RNP (ribonucleoprotein) antibodies.(1,2) Sm is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENA). The other ENA are RNP, SS-A/Ro, and SS-B/La. Each ENA is composed of 1 or more proteins associated with small nuclear RNA species (snRNA) ranging in size from 80 to approximately 350 nucleotides. Antibodies to ENA are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive. Testing for Sm antibodies is not useful in patients without demonstrable antinuclear antibodies.

Interpretation: A positive result for anti-Sm antibodies is consistent with a diagnosis of lupus erythematosus.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


SMADZ

SMAD4 Gene, Full Gene Analysis, Varies

Clinical Information: Juvenile polyposis syndrome (JPS) is a rare hereditary cancer predisposition syndrome caused by variant in the SMAD4 or BMPR1A genes. JPS is characterized by the presence of multiple histologically defined juvenile polyps in the upper and/or lower gastrointestinal (GI) tract and an increased risk for GI cancers. Age of onset for cancer development is typically in the second or third decade of life, although some patients present with a more severe infantile-onset form of the disease. JPS is inherited in an autosomal dominant fashion, although a significant proportion of probands have no family history. Approximately 50% of patients with JPS have an identifiable variant in the SMAD4 or BMPR1A genes. Of note, some patients with variants in the SMAD4 gene exhibit a combined juvenile polyposis/hereditary hemorrhagic telangiectasia phenotype (JP/HHT). Clinical features of HHT include development of arteriovenous malformations (AVMs) of the skin, mucosa, and viscera; spontaneous, recurrent epistaxis (nosebleeds); as well as additional complications such as transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage.

Useful For: Confirmation of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia for patients with clinical features

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known,
predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**SLL 65884**

**Small Lymphocytic Lymphoma, FISH, Tissue**

**Clinical Information:** Small lymphocytic lymphoma (SLL) is the nonleukemic form of chronic lymphocytic leukemia (CLL), the most common adult leukemia in North America. The most common cytogenetic abnormalities detected in CLL are deletions of 6q, 11q, 13q, and 17p, trisomy 12, and the occasional occurrence of IGH translocations at 14q32. Cytogenetics has proven to be a reliable predictor of outcome for patients with CLL. It is unknown if SLL has the same prognostic significance when these genetic abnormalities are observed. This FISH test detects an abnormal clone in approximately 65% of patients with SLL. Patients with t(11;14)(q13;q32) associated with CCND1/IGH fusion, have mantle cell lymphoma which can be distinguished from SLL and other B-cell lymphomas with this assay. Patients with t(14;19)(q32;q13.3) associated with IGH/BCL3 fusion, may have an atypical form of SLL or another low-grade B-cell lymphoma.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with small lymphocytic lymphoma (SLL) and other low-grade B-cell lymphomas Distinguishing patients with 11;14 translocations who have mantle cell lymphoma from patients who have SLL

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. A positive result is not diagnostic for small lymphocytic lymphoma, but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**DHCRZ 608025**

**Smith Lemli Optiz, DHCR7 Gene, Full Gene Analysis, Varies**

**Clinical Information:** Cholesterol plays an essential role in many cellular and developmental
processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play important roles in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive.

Smith-Lemli-Opitz syndrome (SLO) is an autosomal recessive disorder caused by alterations in the DHCR7 gene leading to a deficiency of the 7-dehydrocholesterol reductase enzyme. It is characterized biochemically by markedly increased plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) levels. Clinically, features can include microcephaly, growth retardation, developmental delay, dysmorphic facial features, cleft palate, limb abnormalities (especially 2-3 syndactyly of the toes and postaxial polydactyly), and heart and kidney malformations. The clinical spectrum ranges from mild to severe, with some mildly affected individuals presenting with only 2 to 3 toe syndactyly and mild cognitive impairment. SLO is inherited in an autosomal recessive manner, caused by pathogenic variants in both alleles of the DHCR7 gene. The reported incidence is from 1 in 20,000 to 1 in 40,000, but it may be more prevalent due to underdiagnosis of mildly affected individuals. Measurement of cholesterol precursors in plasma (SLO/Smith-Lemli-Opitz Screen, Plasma) should be performed as a first-tier test to screen for SLO. Cholesterol supplementation may result in clinical improvement, but is not curative.

**Useful For:** Follow up for abnormal biochemical results suggestive of Smith-Lemli-Opitz syndrome
Establishing a molecular diagnosis for patients with Smith-Lemli-Opitz syndrome
Identifying alterations within DHCR7 allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Smith-Lemli-Opitz Screen, Plasma**

**Clinical Information:** Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play important roles in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive.

Smith-Lemli-Opitz syndrome (SLO) is an autosomal recessive disorder caused by variants in the DHCR7 gene leading to a deficiency of the 7-dehydrocholesterol reductase enzyme. It is characterized biochemically by markedly increased plasma concentrations of 7-dehydrocholesterol (7-DHC) and
8-dehydrocholesterol (8-DHC) levels. Clinically, features can include microcephaly, growth retardation, developmental delay, dysmorphic facial features, cleft palate, limb abnormalities (especially 2-3 syndactyly of the toes and postaxial polydactyly), and heart and kidney malformations. However, the clinical spectrum ranges from mild to severe with some mildly affected individuals presenting with only 2 to 3 toe syndactyly and mild cognitive impairment. The reported incidence is between 1 in 10,000 and 1 in 60,000, but it may be more prevalent due to underdiagnoses of mildly affected individuals. Other disorders of cholesterol biosynthesis, including desmosterolosis (desmosterol reductase deficiency) and sitosterolemia, may present with similar manifestations. These disorders can be detected biochemically by performing a quantitative profile of plasma sterols (STER / Sterols, Plasma).

Useful For: Diagnosis of Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)

Interpretation: Elevated plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) are highly suggestive of a biochemical diagnosis of Smith-Lemli-Opitz (SLO). Mild elevations of these cholesterol precursors can be detected in patients with hypercholesterolemia and patients treated with some antipsychotic or antidepressant medications including haloperidol, aripiprazole, and trazodone. However, the 7-DHC to cholesterol ratio is typically elevated only in SLO patients.

Reference Values:
7-DEHYDROCHOLESTEROL
< or =2.0 mg/L

8-DEHYDROCHOLESTEROL
< or = 0.3 mg/L

copies of SMN2 that are present, and 3 or more SMN2 copies are associated with a milder SMA phenotype. This test aims to specifically identify nucleotide variants in SMN1 by direct sequencing and to distinguish these nucleotide variants from changes within SMN2. However, SMN1 exon 1 variants are still unable to be distinguished from changes within SMN2 exon 1.

Useful For: Confirming a diagnosis of spinal muscular atrophy due to nucleotide variants in SMN1 gene Second-tier carrier screening when there is a family history of spinal muscular atrophy, but an affected individual is not available for testing, or when disease-causing variants are unknown Second-tier carrier screening for the reproductive partner of a known SMA carrier

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Smooth Muscle Antibody Screen, Serum

Clinical Information: Autoimmune hepatitis (AIH) is caused by chronic inflammation within the liver, resulting in damage to the hepatocytes.(1) Initially, patients with AIH may be clinically asymptomatic, usually identified only through an incidental finding of abnormal liver function tests. At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies. There are several autoantibodies associated with AIH, although the most common are smooth muscle antibodies (SMA). SMA are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of SMA in the context of AIH has been identified as filamentous-actin (F-actin).(2) Because the clinical symptoms of AIH are nonspecific, being found in a variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(3) The combination of autoantibody serology, specifically SMA and anti-F-actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis.

Useful For: Evaluating patients with chronic liver disease in whom the diagnosis of chronic active autoimmune hepatitis is suspected

Interpretation: Seropositivity for smooth muscle antibodies (SMA) is consistent with a diagnosis of
autoimmune hepatitis (AIH). A negative result for SMA does not exclude a diagnosis of AIH.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

**Smooth Muscle Antibody Titer, Serum**

**Clinical Information:** Autoimmune hepatitis (AIH) is caused by chronic inflammation within the liver, resulting in damage to the hepatocytes.(1) Initially, patients with AIH may be clinically asymptomatic, usually identified only through an incidental finding of abnormal liver function tests. At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies. There are several autoantibodies associated with AIH, although the most common are smooth muscle antibodies (SMA). SMA are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of SMA in the context of AIH has been identified as filamentous-actin (F-actin).(2) Because the clinical symptoms of AIH are nonspecific, being found in a variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(3) The combination of autoantibody serology, specifically SMA and anti-F-actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis.

**Useful For:** Antibody titer testing as a part of evaluating patients with chronic liver disease in whom the diagnosis of chronic active autoimmune hepatitis is suspected

**Interpretation:** Seropositivity for smooth muscle antibodies (SMA) is consistent with a diagnosis of autoimmune hepatitis (AIH). A negative result for SMA does not exclude a diagnosis of AIH.

**Reference Values:**
Only orderable as part of a reflex. For more information see SMAS / Smooth Muscle Antibody Screen, Serum.

Negative
Reference values apply to all ages.

**Clinical References:**

**Smoothelin Immunostain, Technical Component Only**

**Clinical Information:** Smoothelin is a smooth muscle-specific marker expressed only in terminally differentiated smooth muscle cells as part of the cytoskeleton. It is expressed normally in the smooth muscle of the muscularis of the bowel as well as in smooth muscle in other organs.

**Useful For:** Distinguishing muscularis mucosae from muscularis propria
**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FCRNS 57961 Smut Corn (Ustilago maydis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**SNAIL 82344 Snail, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to snail Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L   Interpretation
0     Negative
1     0.35-0.69  Equivocal
2     0.70-3.49  Positive
3     3.50-17.4  Positive
4     17.5-49.9  Strongly positive
5     50.0-99.9  Strongly positive
6     > or =100  Strongly positive

Reference values apply to all ages.


Sodium, 24 Hour, Urine

Clinical Information: Sodium (Na+) is the primary extracellular cation. Sodium is responsible for almost one half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl) which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/day, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Sodium is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules, with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

Useful For: Assessing acid-base balance, water balance, water intoxication, and dehydration

Interpretation: Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night, being only 20% of the peak rate during the day. Sodium may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values <10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to non-kidney causes.

Reference Values:
> or =18 years: 22-328 mmol/24 hours

Reference values have not been established for patients who are less than 18 years of age.


Sodium, Fetal, Random, Urine

Clinical Information: Sodium (Na+) is the primary extracellular cation. Na+ is responsible for
almost one-half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. Excess Na+ is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Na+ is freely filtered by the glomeruli. In mature kidneys, approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine. However, little is known about Na+ excretion in fetal urine.

**Useful For:** Assessing the sodium concentration in fetal urine

**Interpretation:** Fetal urine sodium can be used in conjunction with other fetal urinary analytes to predict fetal renal function, though the utility of this is still under investigation. See Clinical References to guide interpretation, acknowledging the limitations of the available data.

**Reference Values:**
No established reference values.

Random urine sodium may be interpreted in conjunction with serum sodium, using both values to calculate fractional excretion of sodium.

The calculation for fractional excretion (FE) of sodium is:

\[
\text{FE(Na)} = \frac{([\text{Na(urate)}] \times \text{Creat(serum)}) - ([\text{Na(urate)}] \times \text{Creat(serum)})}{([\text{Na(serum)}] \times \text{Creat(urate)})} \times 100
\]

**Clinical References:**
Na+ may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values less than 10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to non-kidney causes.

**Reference Values:**
No established reference values.
Random urine sodium may be interpreted in conjunction with serum sodium, using both values to calculate fractional excretion of sodium.

The calculation for fractional excretion (FE) of sodium (Na) is
\[ \text{FE(Na)} = \left( \frac{\text{Na(urate)} \times \text{Creat(serum)}}{\text{Na(serum)} \times \text{Creat(urate)}} \right) \times 100 \]


**Sodium, Serum**

**Clinical Information:** Sodium is the primary extracellular cation. Sodium is responsible for almost one-half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of sodium in the body is a reflection of the balance between sodium intake and output. Hyponatremia (low sodium) is a predictable consequence of decreased intake of sodium, particularly that precipitated or complicated by unusual losses of sodium from the gastrointestinal tract (eg, vomiting and diarrhea), kidneys, or sweat glands. Renal loss may be caused by inappropriate choice, dose, or use of diuretics; by primary or secondary deficiency of aldosterone and other mineralocorticoids; or by severe polyuria. It is common in metabolic acidosis. Hyponatremia also occurs in nephrotic syndrome, hypoproteinemia, primary and secondary adrenocortical insufficiency, and congestive heart failure. Symptoms of hyponatremia are a result of brain swelling and range from weakness to seizures, coma, and death. Hypernatremia (high sodium) is often attributable to excessive loss of sodium-poor body fluids. Hypernatremia is often associated with hypercalcemia and hypokalemia and is seen in liver disease, cardiac failure, pregnancy, burns, and osmotic diuresis. Other causes include decreased production of antidiuretic hormone (ADH; also known as vasopressin) or decreased tubular sensitivity to the hormone (ie, diabetes insipidus), inappropriate forms of parenteral therapy with saline solutions, or high salt intake without corresponding intake of water. Hypernatremia occurs in dehydration, increased renal sodium conservation in hyperaldosteronism, Cushing syndrome, and diabetic acidosis. Severe hypernatremia may be associated with volume contraction, lactic acidosis, and increased hematocrit. Symptoms of hypernatremia range from thirst to confusion, irritability, seizures, coma, and death.

**Useful For:** Assessing acid-base balance, water balance, water intoxication, and dehydration

**Interpretation:** Symptoms of hyponatremia depend primarily upon the rate of change in sodium concentration, rather than the absolute level. Typically, sodium values less than 120 mEq/L result in weakness; values less than 100 mEq/L result in bulbar or pseudobulbar palsy; and values between 90 and 105 mEq/L result in severe signs and symptoms of neurological impairment. Symptoms associated with hypernatremia depend upon the degree of hyperosmolality present.

**Reference Values:**
<1 year: not established
> or =1 year: 135-145 mmol/L

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company. Philadelphia, PA, 1994

**SOLEF**

**Sole, IgE, Serum**
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to sole Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**CAPN 35594**

**Solid Tumor-Targeted Cancer Gene Panel, Next-Generation Sequencing, Varies**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify variants across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common variants in 50 genes known to be associated with cancer. ... See Targeted Gene Regions Interrogated by Solid Tumor Targeted Cancer Gene
Panel by Next-Generation Sequencing in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying solid tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously. Identifying specific variants within genes known to be associated with response or resistance to specific cancer therapies. Identifying variants that may help determine prognosis for patients with solid tumors. Assisting in establishing a diagnosis (eg, KIT and PDGFRA alterations for gastrointestinal stromal tumors). Aiding in the determination of clinical trial eligibility for patients with genetic variants not amenable to current FDA-approved targeted therapies. This test is not intended for use for hematological malignancies or assessment of germline variants.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FSFM 58015**

**Soluble Fibrin Monomer**

**Reference Values:**
Negative

**SOLFM 602175**

**Soluble Fibrin Monomer, Plasma**

**Clinical Information:** Fibrin monomers are intermediate products formed during the proteolysis of fibrinogen by thrombin. During intravascular coagulation, low levels of thrombin are available in the blood, but the quantity of fibrin monomers formed are not sufficient to aggregate and form a clot; instead, they associate themselves with fibrinogen or fibrinogen-degradation products to form soluble complexes (ie, soluble fibrin monomer complex: SFMC). Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation: DIC is a clinical diagnosis; no single test is completely sensitive or specific for ICF.

**Useful For:** Assisting in the diagnosis of arterial or venous prethrombotic states in various pathological and clinical situations including disseminated intravascular coagulation (DIC) and postoperative monitoring of surgeries with a high risk of thromboses.

**Interpretation:** A normal soluble fibrin monomer complex (SFMC) does not exclude the presence of thrombosis or early disseminated intravascular coagulation (DIC)/intravascular coagulation and fibrinolysis (ICF). An elevated SFMC may be seen in patients with venous or arterial thromboembolism or DIC/ICF. It may also be mildly elevated in clotted specimens.

**Reference Values:**
Only orderable as part of a coagulation reflex. For more information see:
- ALUPP / Lupus Anticoagulant Profile, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- AATHR / Thrombophilia Profile, Plasma
- APROL / Prolonged Clot Time Profile, Plasma
- ADIC / Disseminated Intravascular Coagulation/ Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

< or =8 mcg/mL
**Clinical References:**


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**Soluble Liver Antigen (SLA) Autoantibody**

**Clinical Information:** Anti-soluble liver antigen antibodies are detected in 10-30% of patients with type 1 autoimmune hepatitis (AIH), but not in patients with type 2 AIH, primary sclerosing cholangitis or primary biliary cirrhosis. The antibody is directed against a UGA suppressor tRNA associated protein. In some patients with AIH, this antibody may be the only autoantibody detected by current assays.

**Reference Values:**

Reference Range: Negative 0.0-20.0 U

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>20.1-24.9 U</td>
<td>equivocal</td>
</tr>
<tr>
<td>&gt;25.0 U</td>
<td>positive</td>
</tr>
</tbody>
</table>

Antibodies to soluble liver antigen (SLA) appear to be directed against the UGA-suppressor tRNA associated protein. These antibodies are highly specific for autoimmune hepatitis (AIH) and may rarely, be the only autoantibodies detected in serum from such patients. Antibodies to SLA are most closely associated with AIH type 1; the presence of these antibodies suggests that these patients may have AIH type 1.

Anti-SLA antibodies may be detected in some patients with the primary biliary cirrhosis-AIH overlap syndrome, but not in healthy controls.

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**Soluble Transferrin Receptor (sTfR), Serum**

**Clinical Information:** Iron uptake into cells is mediated through internalizing iron-transferrin complexes. The iron-transferrin complex binds to transferrin receptors present on the external face of the plasma membrane, and is internalized through endosomes with ultimate release of iron into the cytoplasm. Plasma membrane-bound transferrin receptor is released by proteolytic cleavage of the extracellular domain, resulting in the formation of a truncated soluble transferrin receptor (sTfR) that circulates freely in the blood. The concentration of sTfR is an indicator of iron status. Iron deficiency causes overexpression of transferrin receptor and sTfR levels, while iron repletion results in decreased sTfR levels. While ferritin measurement is the accepted method for assessment of iron deficiency, ferritin is an acute-phase reactant and elevates in response to processes that do not correlate with iron status, including inflammation, chronic disease, malignancy, and infection. sTfR is not an acute-phase reactant and the interpretation of iron status using sTfR measurement is not affected by these confounding pathologies.

**Useful For:** Evaluation of suspected iron deficiency in patients who may have inflammation, infection, or chronic disease and other conditions in which ferritin concentration does not correlate with iron status, including:
- Cystic fibrosis patients who frequently have inflammation or infections(1-2)
- Evaluating insulin-dependent diabetics who may have iron-deficiency resulting from gastric autoimmunity and atrophic gastritis(3)

**Interpretation:** Soluble transferrin receptor (sTfR) concentrations are inversely related to iron status; sTfR elevates in response to iron deficiency and decreases in response to iron repletion.

**Reference Values:**

1.8-4.6 mg/L

It is reported that African Americans may have slightly higher values.

**Clinical References:**


**Solute Carrier Organic Anion Transporter Family Member 1B1 (SLCO1B1) Genotype, Statin, Varies**

**Clinical Information:** The most common adverse drug reaction associated with statins is skeletal muscle toxicity, which can include myalgia (with and without elevated creatine kinase levels), muscle weakness, muscle cramps, myositis, and rhabdomyolysis. (1) Rhabdomyolysis, while rare, is of clinical concern because of the risk for death as a result of cardiac arrhythmia, renal failure, and disseminated intravascular coagulation. While the underlying causes of statin-associated myopathy are not known, several hypotheses have been formulated, including those related to the biochemical pathway of cholesterol synthesis inhibition and statin metabolism. SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) influx transporter located on the basolateral membrane of hepatocytes. OATP1B1 facilitates the hepatic uptake of statins as well as other endogenous compounds (eg, bilirubin). Changes in the activity of this transporter (eg, through genetic variations or drug-drug interactions) can increase the severity of statin-associated myopathy (ie, statin intolerance). (2) SLCO1B1 rs4149056 (c.521T>C, p.V174A), which is found in *5, *15, and *17, interferes with localization of the transporter to the plasma membrane and can lead to increased systemic statin concentrations. (3-4) All statins are substrates of OATP1B1, but the association of SLCO1B1 c.521T>C with statin intolerance varies depending on statin and dose and is most pronounced with higher doses of simvastatin therapy. A case-control study of simvastatin-induced myopathy observed an odds ratio (OR) for myopathy of 4.5 for *5 heterozygotes and 16.9 for *5 homozygotes (compared to individuals who did not carry *5) among patients receiving high-dose (80 mg/day) simvastatin therapy. (4) A dose relationship was also demonstrated in a replication cohort of patients taking 40 mg/day simvastatin with a relative risk of 2.6 per copy of the *5 allele. While the SLCO1B1 c.521T>C genotype has also been shown to affect systemic exposure of other statins (eg, atorvastatin, pravastatin, rosuvastatin) in addition to simvastatin, (3) there is less evidence demonstrating a clinical association between the SLCO1B1 genotype and myopathy with statins other than simvastatin. (2) SLCO1B1 rs4149015 (c.-910G>A), which is found in *17 and *21, is associated with increased pravastatin blood levels and a reduced lipid lowering effect but has not been associated with statin-induced myopathy or rhabdomyolysis. A frequency of the SLCO1B1 alleles varies across different racial and ethnic groups.

**Useful For:** Predicting risk for statin-associated myopathy in patients beginning statin therapy, especially simvastatin therapy Determining a potential statin lipid lowering response, especially when using pravastatin

**Interpretation:** An interpretive report will be provided. The complementary DNA positions are based on NM_006446.4. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**

An interpretive report will be provided.

SOMAT 70553

**Somatostatin (SOMATO) Immunostain, Technical Component Only**

**Clinical Information:** Somatostatin is a cyclic polypeptide hormone originally isolated from the hypothalamus and characterized by its ability to inhibit the release of growth hormone from the pituitary. In the digestive system, somatostatin production occurs in the intrinsic nerves of the intestinal wall, endocrine cells of the digestive mucosa, and in the D-cells of pancreatic islets. Antibodies to somatostatin can be used to characterize pancreatic islet cell tumors or other neuroendocrine tumors.

**Useful For:** Aids in the characterization of pancreatic islet cell tumors or other neuroendocrine tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

FSOMA 90172

**Somatostatin (Somatotropin Release-Inhibiting Factor, SRIF)**

**Clinical Information:** Somatostatin is a cyclic peptide originally isolated from sheep hypothalami and shown to inhibit the release of Growth Hormone. Somatostatin is present primarily in three main forms: a 14 amino acid peptide, a 28 amino acid peptide (ProSomatostatin), and a 12,000 molecular weight ProSomatostatin. This assay measures only the 14 amino acid form of Somatostatin. All three forms of Somatostatin have similar biological properties and overall potencies. Somatostatin is a physiological regulator of islet cell and gastrointestinal functions, and is a suppressor of many pituitary hormones including Growth Hormone, Prolactin, and Thyrotropin (TSH). Somatostatin levels are often elevated in diabetics, but the levels return to normal upon correction of the hormonal and metabolic deficiencies present. In many cases of APUDomas including VIPoma, Insulinoma, Glucagonoma, and Gastrinoma, elevated levels of Somatostatin are found.

**Reference Values:**
Up to 25 pg/mL

SSTR2 113597

**Somatostatin Receptor 2 (SSTR2), Immunostain, Technical Component Only**
**Clinical Information:** Somatostatin receptor 2 (SSTR2) is expressed in the secretory cells of the pancreas and the neurons of the central nervous system. SSTR2 is overexpressed in neuroendocrine tumors (NET) and can help predict response to targeted radiopeptide therapy. SSTR2 expression can also play a role in guiding imaging studies and treatment choice.

**Useful For:** Aids in the identification of neuroendocrine tumors

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Sotalol (Betapace)**

**Reference Values:**
Reference Range: 500 - 4000 ng/mL

Serum Sotalol concentrations producing beta-blockade:
500 - 4000 ng/mL

Toxic range has not been established.

**SOX10 Immunostain, Technical Component Only**

**Clinical Information:** SOX10 is a nuclear transcription factor that plays an important role in schwannian and melanocytic cell differentiation, and has been shown to be a useful marker in the diagnosis of melanocytic and schwannian tumors. SOX10 is expressed in benign melanocytic naevi and melanomas, including desmoplastic melanoma and spindle cell melanoma. It is also expressed by tumors with schwannian differentiation, including malignant peripheral nerve sheath tumors, Schwannomas, and neurofibromas. SOX10 is expressed in normal tissues, including Schwann cells, melanocytes, and myoepithelial cells of salivary, bronchial, and mammary glands.

**Useful For:** Identification of malignant melanomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
SOX11 Immunostain, Technical Component Only

**Clinical Information:** SOX11 is a transcription factor involved in embryonic neurogenesis and tissue remodeling. Nuclear SOX11 is expressed in most B- and T-lymphoblastic leukemia/lymphomas and a proportion of Burkitt lymphomas, but only weakly expressed in some hairy cell leukemias. Mantle cell lymphomas (MCL) show SOX11 expression and it has been suggested to correlate with overall survival.

**Useful For:** Identification of mantle cell lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
1. Chen YH, Gao J, Fan G, Peterson LC: Nuclear expression of sox11 is highly associated with mantle cell lymphoma but is independent of t(11;14)(q13;q32) in non-mantle cell B-cell neoplasms. Mod Pathol 2010;23:105-112

**Soybean IgG**

**Interpretation:**

**Reference Values:** Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Soybean IgG4**

**Reference Values:**

Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Soybean, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to soybean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical Information:** The presence or absence of a cellular antigen is an inherited trait. As a general rule, individuals will not make antibody directed against an antigen present on their own red blood cells.

**Useful For:** Additional proof of alloantibody specificity This test is not useful for the purpose of establishing paternity Determining possible antibody specificities in complex cases

**Interpretation:** Each antigen typed will be listed by name, followed by "pos or +" indicating that the antigen is present, or by "neg or -" indicating that the antigen is absent.

**Reference Values:**
Reported as positive or negative


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**SS1PO**
**Special Stain Group I, Microorganism, Profile Only (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**SS3PO**
**Special Stain Group III, Enzyme, Profile Only (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**SS1PC**
**Special Stain, Group I, Microorganisms (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**SS2PC**
**Special Stain, Group II, Other, (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**SS2PO**
**Special Stain, Group II, Other, Profile Only (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**SS3PC**
**Special Stain, Group III, Enzyme (Bill Only)**
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
Specific Gravity, Random, Urine

**Clinical Information:** Specific gravity (SG), the ratio of the mass of a solution compared to the mass of an equal volume of water, is an estimate of the concentration of substances dissolved in the solution. Urine SG can be used to assess the kidney's ability to concentrate or dilute urine. However, because protein, glucose, and contrast dye have molecular masses that are relatively large compared to other major components of urine (eg, sodium, chloride, potassium), they disproportionately affect SG. In these cases, urine osmolality is a better measure of urine concentration.

**Useful For:** As a partial assessment of the kidney's ability to concentrate urine

**Interpretation:** Low specific gravity (SG) (1.001-1.003) may indicate the presence of diabetes insipidus, a disease caused by impaired functioning of antidiuretic hormone (ADH). Low SG also can occur in patients with glomerulonephritis, pyelonephritis, and other renal abnormalities. In these cases, the kidney has lost its ability to concentrate due to tubular damage. High SG may occur in patients with adrenal insufficiency, hepatic disease, congestive heart failure, or in patients experiencing excessive water loss due to sweating, fever, vomiting, or diarrhea.

**Reference Values:**
1.002-1.030

**Clinical References:**

Specimen Identification by PCR (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Specimen Source Identification

**Clinical Information:** For various reasons, the patient origin for a particular specimen may be questioned. This is especially true for paraffin-embedded material: labeling accuracy may be questioned or tissue from other sources may be included by mistake. Confirmation of the patient origin may be critical to the clinical workup of that patient. Molecular methods are now available to extract DNA from various sources, including paraffin-embedded material, and to compare the molecular fingerprint (genotype) of one specimen source with another one. Matching genotypes on multiple specimens suggest that they are derived from the same patient, whereas differences in genotype suggest different patient sources.

**Useful For:** Determining specimen origin when the patient identity of a specimen is in question

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

SpecStain, frozen (Bill Only)

**Reference Values:**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Spinach IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Spinach, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to spinach Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's
**Clinical Information:** Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics (ACMG) and The American College of Obstetricians and Gynecologists (ACOG) currently recommend offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy. The most common form of SMA is associated with the loss of Survival Motor Neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the SMN1 gene but a small portion of SMN is also contributed by the SMN2 gene. In fact, SMN1 produces more than 90% of SMN protein, while SMN2 produces about less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotide changes, 1 of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 have been observed. In addition, individuals may also have 0 to 5 copies of SMN2. SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a point mutation in the other allele. The severity of a patient's disease is associated with the number of copies of SMN2 that are present and 3 or more SMN2 copies are associated with a milder SMA phenotype. As the SMA test is a quantitative assay for the number of SMN1 exon 7 deletions, any result showing 2 SMN1 copies may in fact have 2 normal copies of SMN1 in cis (on the same chromosome) and a copy of SMN1 with the exon 7 deletion on the other chromosome (in trans). This is called the "2+0" carrier genotype. The frequency of the "2+0" carrier genotype differs by ancestry. Previously, it was not possible to distinguish a "2+0" carrier from an individual with 1 copy of SMN1 on each chromosome. However, following a study performed by Luo et al,(6) it is now possible to provide an adjusted genetic residual carrier risk specific to oneâ€™s ancestry, based on the presence or absence of the SMN1 polymorphism g.27134T>G. The presence of this polymorphism is linked to being a "2+0" carrier in the Ashkenazi Jewish and Asian populations and it increases the chances that one is a "2+0" carrier in other populations. Please see the table below for details. SMA carrier residual risk estimates.(6)Â Ancestry Carrier frequency Detection rate based on copy number alone Residual risk after detection of 2 copies of SMN1 Detection rate with addition of SMN1 g.27134T>G Residual risk of being a 2+0 carrier after absence of SMN1 g.27134T>G Residual risk of being a 2+0 carrier after presence of SMN1 g.27134T>G Ashkenazi Jewish 1 in 41.1 90% 1 in 345 94% 1 in 580 2+0 Carrier Asian 1 in 53 92.6% 1 in 628 93.3% 1 in 701.8 2+0 Carrier African American 1 in 66 71.1% 1 in 121 N/A 1 in 395.7 1 in 33.5 Hispanic 1 in 117 90.6% 1 in 1,061 N/A 1 in 1,762 1 in 139.6 Caucasian 1 in 35 94.9% 1 in 632 N/A 1 in 769.3 1 in 28.6

**Useful For:** General population carrier screening for spinal muscular atrophy (SMA) Carrier screening for reproductive partners of known SMA carriers Carrier screening for parents of a child with a known deletion of the survival motor neuron 1 gene (SMN1) or other family history of SMA

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

Spinal Muscular Atrophy Diagnostic Assay, Deletion/Duplication Analysis, Varies

Clinical Information: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (Type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics (ACMG) and The American Congress of Obstetricians and Gynecologists (ACOG) currently recommend offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy.

The most common form of SMA is associated with the loss of survival motor neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the SMN1 gene but a small portion of SMN is also contributed by the SMN2 gene. In fact, SMN1 produces more than 90% of SMN protein, while SMN2 produces less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotide changes, 1 of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 have been observed. In addition, individuals may also have 0 to 5 copies of SMN2. SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a point mutation in the other allele. The severity of a patient's disease is associated with the number of copies of SMN2 that are present and 3 or more SMN2 copies are associated with a milder SMA phenotype. As the SMA test is a quantitative assay for the number of SMN1 exon 7 deletions, any result showing 2 or more SMN1 copies may, in fact, have 2 copies of SMN1 in cis (on the same chromosome) and a copy of SMN1 with the exon 7 deletion on the other chromosome (in trans). This is called the "2+0" carrier genotype. The frequency of the "2+0" carrier genotype differs by ancestry. Previously, it was not possible to distinguish a "2+0" carrier from an individual with 1 copy of SMN1 on each chromosome. However, following a study performed by Luo et al., it is now possible to provide an adjusted genetic residual carrier risk specific to one's ancestry, based on the presence or absence of the SMN1 polymorphism g.27134T>G. The presence of this polymorphism is linked to being a "2+0" carrier in the Ashkenazi Jewish and Asian populations and it increases the chances that one is a "2+0" carrier in other populations. Please see the table below for details. SMA carrier residual risk estimates. (6)

| Ancestry      | Carrier frequency | Detection rate based on copy number alone | Residual risk after detection of 2 copies of SMN1 | Residual risk after addition of SMN1 g.27134T>G | Residual risk of being a 2+0 carrier after absence of SMN1 g.27134T>G | Residual risk of being a 2+0 carrier after presence of SMN1 g.27134T>G | Ashkenazi Jewish 1 in 41.1 | 90% 1 in 345 94% 1 in 580 2+0 Carrier Asian 1 in 53 92.6% 1 in 628 93.3% 1 in 701.8 2+0 Carrier African American 1 in 66 71.1% 1 in 121 N/A 1 in 395.7 1 in 33.5 Hispanic 1 in 117 90.6% 1 in 1,061 N/A 1 in 1,762 1 in 139.6 Caucasian 1 in 35 94.9% 1 in 632 N/A 1 in 769.3 1 in 28.6 |
|---------------|-------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------------|------------------------------------------------|-----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|

Useful For: First-tier newborn screening for spinal muscular atrophy (SMA) Prenatal testing for SMA Diagnostic testing to confirm a suspected diagnosis of SMA

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

Spinobulbar Muscular Atrophy (Kennedy Disease), Molecular Analysis, Varies

Clinical Information: X-linked spinal and bulbar muscular atrophy (spinobulbar muscular atrophy: SBMA; or Kennedy disease) is characterized by onset of progressive muscle weakness, atrophy, and fasciculations typically in the fourth or fifth decade of life. Affected patients also have signs of androgen insensitivity such as gynecomastia, reduced fertility, and testicular atrophy. The clinical severity and age at onset can be quite variable, even within families. Because this is an X-linked disease, males manifest this disorder and females are generally asymptomatic carriers. However, there have been reports of female carriers who exhibit symptoms such as muscle weakness and cramping. SBMA is caused by an expansion of the CAG trinucleotide repeat in exon 1 of the human androgen receptor (AR) gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 11 to 34. The number of repeats found in affected individuals can range from 38 to 62. There is no consensus as to the clinical significance of alleles of 35 CAG repeats and literature suggests that alleles of 36 to 37 CAG repeats may be associated with reduced penetrance. As with other trinucleotide repeat disorders, anticipation is frequently observed and larger CAG expansions are associated with earlier onset and a more rapid clinical progression.

Useful For: Molecular confirmation of clinically suspected cases of sporadic or familial spinobulbar muscular atrophy (SBMA) Presymptomatic testing for individuals with a family history of SBMA and a documented expansion in the androgen receptor (AR) gene

Interpretation: An interpretive report will be provided.

Reference Values:
Normal alleles: 11-34 CAG repeats
Abnormal alleles: 36-62 CAG repeats

An interpretive report will be provided.


Sporothrix Antibody, Serum

Clinical Information: Sporotrichosis is an endemic fungal infection caused by the dimorphic fungus Sporothrix schenckii. Most cases of sporotrichosis have been reported from the subtropical and tropical regions of the Americas, but a global distribution is likely. The organism is often isolated from soil, plants, or plant products (wood), and occupational or recreational exposure to these materials is often implicated in infected individuals. Infections due to S schenckii can be differentiated into several distinct syndromes: -The cutaneous form of the disease is most common, often arising from sites of minor skin trauma. The primary erythematous, papulonodular lesion may range from several...
millimeters to 4 cm in size. Secondary lesions develop proximally along lymphatic channels. These generally painless lesions usually do not involve lymph nodes, although lymphadenopathy may develop.

-Extracutaneous sporotrichosis can be manifested as osteoarticular involvement of a single joint. Major joints of the extremities (ankle, knee, elbow, hand) are most often involved. The affected joint is swollen and painful, with an attendant effusion. Systemic symptoms are minimal. -Pulmonary sporotrichosis with cavitary lesions also has been described. -A multifocal extracutaneous syndrome has been described, consisting of multijoint involvement, or widely scattered cutaneous lesions.

Constitutional symptoms (fever, weight loss) are often noted, and spread to bone and central nervous system may occur. Underlying immune system suppression is often a contributing factor. Untreated infection is ultimately fatal.(1)

**Useful For:** Aiding in the diagnosis of extracutaneous sporotrichosis

**Interpretation:** Extracutaneous infections, including disseminated and articular infections, produce positive tests. The test should be positive in approximately 90% to 95% of all primary sporotrichosis infections. Specimens from these patients may become positive by 2 weeks after infection and are not expected to remain positive for more than 7 months after the original primary infection. Agglutination titers of 1:8 and higher indicate presumptive evidence of sporotrichosis. Titers of 1:4 to 1:8 are commonly seen in normal persons. Some cutaneous infections are associated with negative serologic results.

**Reference Values:**

- Negative

**Clinical References:**


**Sporothrix Antibody, Spinal Fluid**

**Clinical Information:** Sporotrichosis is an endemic fungal infection caused by the dimorphic fungus Sporothrix schenckii. Most cases of sporotrichosis have been reported from the subtropical and tropical regions of the Americas, but a global distribution is likely. The organism is often isolated from soil, plants, or plant products (wood), and occupational or recreational exposure to these materials is often implicated in infected individuals. Infections due to S schenckii can be differentiated into several distinct syndromes: -The cutaneous form of the disease is most common, often arising from sites of minor skin trauma. The primary erethematous papulonodular lesion may range from several millimeters to 4 cm in size. Secondary lesions develop proximally along lymphatic channels. These generally painless lesions usually do not involve lymph nodes, although lymphadenopathy may develop. -Extracutaneous sporotrichosis can be manifested as osteoarticular involvement of a single joint. Major joints of the extremities (ankle, knee, elbow, hand) are most often involved. The affected joint is swollen and painful, with an attendant effusion. Systemic symptoms are minimal. -Pulmonary sporotrichosis with cavitary lesions also has been described. -A multifocal extracutaneous syndrome has been described, consisting of multijoint involvement, or widely scattered cutaneous lesions. Constitutional symptoms (fever, weight loss) are often noted, and spread to bone and central nervous system may occur. Underlying immune system suppression is often a contributing factor. Untreated infection is ultimately fatal.(1)

**Useful For:** Aiding in the diagnosis of extracutaneous sporotrichosis

**Interpretation:** Any titer should be considered clinically significant; however, clinical correlation must be present. Extracutaneous infections, including disseminated and articular infections, produce positive tests.

**Reference Values:**

- Negative

Reference values apply to all ages.

**Spotted Fever Group Antibody, IgG and IgM, Serum**

**Clinical Information:** Species of Rickettsia are small (0.3-0.5 mcm x 1-2 mcm) obligately intracellular bacteria (Proteobacteria). They have a gram-negative cell wall structure. Rickettsia are found in arthropod hosts for at least part of their life cycle. Rickettsial infections in the United States are caused by 2 major groups within the genus Rickettsia: spotted fever group and typhus fever group. The spotted fever group includes R rickettsii (Rocky Mountain spotted fever), R akari, R conorii (Boutonneuse fever), R australis (Queensland tick typhus), and R sibirica (North Asian tick typhus). The typhus fever group includes R typhi (murine typhus; endemic typhus) and R prowazekii (epidemic typhus). R rickettsiae is the most common rickettsial species encountered in the United States and is transmitted through a tick vector (Dermacentor species or, less commonly, Rhipicephalus sanguineus). Following a 2- to 14-day incubation period, patients most commonly present with fever, chills, and myalgia. A maculopapular rash typically appears 2 to 5 days after fever onset, though approximately 10% of patients will not develop a rash. Antibodies to the spotted fever group agents are detectable within 7 to 10 days after illness onset. Demonstration of either 1) seroconversion or 2) a 4-fold change in IgG-specific antibody titers in acute and convalescent serum samples is consistent with acute or ongoing disease.

**Useful For:** Aids in the diagnosis of spotted fever group rickettsial infections

**Interpretation:** This test detects reactivity to the group-specific rickettsia. For example, antibody reactivity to the Rickettsia rickettsii will also react with other organisms within the spotted fever group. IgG > or =1:256: Serum end point titers of > or =1:256 are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. <1:256 and > or =1:64: -Single serum end point titers > or =1:64 and <1:256 are suggestive of infection at an undetermined time and may indicate either past infection or early response to a recent rickettsial infection. -A 4-fold or greater increase in IgG titer between 2 serum specimens drawn 1 to 2 weeks apart and tested in parallel is considered presumptive evidence of a recent or current infection. -In patients infected with organisms within the rickettsial groups, IgG antibody is generally detectable within 1 to 2 weeks of onset of symptoms, peaking within 1 to 2 months and declining thereafter. Following prompt antimicrobial treatment, titers generally decline below detectable levels within 8 to 11 months. With relapse, prior immunization, or delayed antibiotic treatment, IgG levels may remain elevated for more than a year postonset. IgM > or =1:64: -Titers of > or =1:64 are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. <1:64: -Titers <1:64 suggest that the patient does not have an acute rickettsial infection. -IgM class antibody is transiently detected within 1 to 2 weeks of onset of symptoms, usually declining rapidly within 3 months following prompt antibiotic treatment. These levels will also be elevated for an extended period with relapse, prior immunization, or delayed antibiotic treatment.

**Reference Values:**
IgG: <1:64
IgM: <1:64

Reference values apply to all ages.

Spruce, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to spruce Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Squamous Cell Carcinoma, Serum

**Reference Values:**

0.0-1.7 ng/mL

This test is performed using the BRAHMS SCC Kryptor kit. Results obtained with different assay methods or kits cannot be used interchangeably. SCC antigen levels alone should not be interpreted as evidence of the presence or absence of malignant disease. In patients with known or expected cancer, other tests and procedures must be considered for diagnosis and patient management. Elevated
concentrations may also occur in benign conditions such as gynecological diseases, inflammatory lung disease and liver or renal insufficiency.

**Squash, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to squash Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to squid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**SS-A and SS-B Antibodies, IgG, Serum**

**Clinical Information:** Sjogren syndrome (SS)A (Ro), SSB (La), ribonucleoprotein (RNP), and Smith (Sm) proteins are autoantigens commonly referred to as extractable nuclear antigens (ENA). Antibodies to ENA are common in patients with connective tissue diseases (systemic rheumatic diseases). SSA or Ro is composed of protein antigens of 52 kD and 60 kD combined with cytoplasmic RNA species. SSA antibodies occur in patients with several different connective tissue diseases including Sjogren syndrome, an autoimmune disease that involves primarily the salivary and lacrimal glands (up to 90% of cases); systemic lupus erythematosus (SLE) (40%-60% of cases); and rheumatoid arthritis. SSA antibodies are associated with childhood SLE, neonatal SLE, and with congenital heart block in infants born to mothers with SLE.(1,2) SSA antibodies have also been reported to be associated with features of extravascular inflammation in patients with SLE including vasculitis, purpura, cytophenias, and adenopathy. SSB or La is composed of a 48-kD protein combined with RNA species. SSB antibodies are found primarily in patients with Sjogren syndrome or SLE, where they occur with frequencies of approximately 60% and 15%, respectively.(1,2) SSB antibodies occur only infrequently in the absence of SSA antibodies. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive, especially those with signs and symptoms consistent with Sjogren syndrome or lupus erythematosus This test is not useful in patients without demonstrable
antinuclear antibodies.

**Interpretation:** A positive result for SSA (Ro) or SSB (La) antibodies is consistent with connective tissue disease, including Sjogren syndrome, lupus erythematosus (LE), or rheumatoid arthritis. A positive result for SSA antibodies in a woman with LE prior to delivery indicates an increased risk of congenital heart block in the neonate.

**Reference Values:**

SS-A/Ro ANTIBODIES, IgG

- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

SS-B/La ANTIBODIES, IgG

- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


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**SS-A/Ro Antibodies, IgG, Serum**

**Clinical Information:** SS-A/Ro is an extractable nuclear antigen (ENA) composed of protein antigens of 52 kD and 60 kD combined with cytoplasmic RNA species. SS-A/Ro antibodies occur in patients with several different connective tissue diseases including Sjogren syndrome, an autoimmune disease that involves primarily the salivary and lachrymal glands (up to 90% of cases); lupus erythematosus (LE) (40%-60% of cases); and rheumatoid arthritis. SS-A/Ro antibodies are associated with childhood LE, neonatal LE, and with congenital heart block in infants born to mothers with LE. SS-A/Ro antibodies have also been reported to be associated with features of extraglandular inflammation in patients with LE including vasculitis, purpura, cytopenias, and adenopathy. SS-A/Ro is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENA). The other ENA are SS-B/La, RNP, and Sm. Each ENA is composed of 1 or more proteins associated with small nuclear or cytoplasmic RNA species (snRNP) ranging in size from 80 to 350 nucleotides. Antibodies to ENA are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive. Testing for SS-A/Ro antibodies is not useful in patients without demonstrable antinuclear antibodies.

**Interpretation:** A positive result for SS-A/Ro antibodies is consistent with connective tissue disease, including Sjogren syndrome, lupus erythematosus (LE), or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with LE prior to delivery indicates an increased risk of congenital heart block in the neonate.

**Reference Values:**

- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**

SSB
81359
SS-B/La Antibodies, IgG, Serum

Clinical Information: SS-B/La is an extractable nuclear antigen (ENA) composed of a 48-kD protein combined with RNA species. SS-B/La antibodies are found primarily in patients with Sjogren syndrome or lupus erythematosus (LE), where they occur with frequencies of approximately 60% and 15%, respectively. (1, 2) SS-B/La antibodies occur only infrequently in the absence of SS-A/Ro antibodies. SS-B/La is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENA). The other ENA are SS-A/Ro, RNP, and Sm (Smith). Each ENA is composed of 1 or more proteins associated with cytoplasmic or small nuclear RNA species (snRNA) ranging in size from 80 to 350 nucleotides. Antibodies to ENA are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive. Testing for SS-B/La antibodies is not useful in patients without demonstrable antinuclear antibodies.

Interpretation: A positive result for SS-B/La antibodies is consistent with connective tissue disease, including Sjogren syndrome and lupus erythematosus.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


STLPC
83916
St. Louis Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: Since 1933, outbreaks of St. Louis encephalitis (SLE) have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Infections with arboviruses, including SLE, can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. SLE tends to produce the most severe clinical infections in older persons.

Useful For: Aiding the diagnosis of St. Louis encephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
IgG: <1:1
IgM: <1:1
Reference values apply to all ages.


**STLP 83154**

**St. Louis Encephalitis Antibody, IgG and IgM, Serum**

**Clinical Information:** The onset of St. Louis encephalitis is characterized by generalized malaise, fever, chilliness, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by the meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Areas of outbreaks since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence of St. Louis encephalitis is associated with summer and early autumn.

**Useful For:** Aiding in the diagnosis of St. Louis encephalitis

**Interpretation:** In patients infected with the St. Louis encephalitis virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. A single serum specimen IgG of 1:10 or greater indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). While a 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection. Infections with St. Louis encephalitis can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. St. Louis encephalitis tends to produce the most severe clinical infections in older persons.

**Reference Values:**

- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.


**ST2S 61723**

**ST2, Serum**

**Clinical Information:** Heart failure is a chronic, progressive, complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are readmitted within the forthcoming year, incurring costly treatments and therapies.(1) The development and progression of heart failure is a clinically silent
process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury or stress. (2) Soluble ST2 (sST2) is a biomarker that appears to be actively involved with interleukin (IL)-33 in modulating cardiac remodeling and ventricular function via effects in the inflammatory and apoptosis pathways. (3) ST2 is a member of the IL-1 receptor family and has 2 isoforms that are directly implicated in progression of cardiac disease: sST2 and a transmembrane-bound form, ST2 ligand (ST2L). IL-33 is the hormone that interacts with ST2L, protecting against left ventricular hypertrophy and myocardial fibrosis to effectively preserve cardiac function. Therefore, when sST2 concentrations are high, IL-33 is unavailable for cardioprotective signaling, leaving the heart vulnerable to the effects of sST2. High concentrations of sST2 result in cellular death, tissue fibrosis, reduced cardiac function, and an increase in the rate of disease progression.

**Useful For:** Aiding in prognosis for patients diagnosed with chronic heart failure

**Interpretation:** Clinically, ST2 concentrations in the HF-ACTION heart failure study were a significant predictor of mortality, all-cause hospitalization, mortality due to cardiovascular disease, and hospitalization due to cardiovascular disease using a cut point of 35 ng/mL. In addition, mortality risk was significantly higher in patients with ST2 greater than 35 ng/mL. (4) The risk appears early and persists throughout the follow-up period. Clinical risk categories are substantiated by results from several large chronic heart failure studies: -Low risk: < or =35.0 ng/mL -High risk: >35.0 ng/mL (high risk) Results should be interpreted in the context of the individual patient presentation. Elevated ST2 results indicate an increased risk for adverse outcomes and signal the adverse remodeling and progression of disease. The reference interval was derived from normal donors without a history of cardiovascular disease, stroke, diabetes, renal disease, liver disease, or autoimmune diseases. The reference range is gender dependent; however, it is the clinical cut point that is recognized as providing the most utility. Knowledge of ST2 results in a heart failure patient may assist in cardiovascular risk stratification and lead to more aggressive management. There are no specific ST2 inhibitors available at this time and heart failure patients with elevated ST2 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers and aldosterone antagonists are thought to be particularly effective.

**Reference Values:**

**Males:**
- <24 months: not established
- 2-17 years: < or =43.0 ng/mL
- > or =18 years: < or = 52.0 ng/mL

**Females:**
- <24 months: not established
- 2-17 years: < or =43.0 ng/mL
- > or =18 years: < or =38.7 ng/mL

**Clinical References:**
**Stachybotrys chartarum/atra IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 50.00 Very High Positive 5 >50.00 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

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**Stachybotrys Panel II**

**Reference Values:**

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<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stachybotrys chartarum/atra IgE</td>
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<tr>
<td>Stachybotrys chartarum/atra IgG</td>
<td>&lt;20.4 mcg/mL</td>
</tr>
<tr>
<td>Stachybotrys chartarum/atra IgA</td>
<td>&lt;1.0 mg/L</td>
</tr>
</tbody>
</table>

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**Staclot Lupus Anticoagulant, Plasma**

**Clinical Information:** Lupus anticoagulant (LA) is one of several antibodies referred to as antiphospholipid antibodies (APA). Lupus anticoagulants are immunoglobulins (IgG, IgM, IgA, or a combination of these) that interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of one or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT; dilute Russell viper venom time: DRVVT due to inhibition). The characteristic in vitro inhibition caused by the presence of LA inhibitors can be overcome by additional phospholipid, which can be used to confirm the presence of LA. The Staclot LA assay system enhances the sensitivity and specificity of APTT-based LA detection by employing: 1. A partial thromboplastin that is more sensitive to LA than many other reagents. 2. Hexagonal (II) phase phosphatidylethanolamine for neutralization of LA inhibition rather than lamellar phase phospholipid. Although LA causes prolonged clotting times in vitro, there is a strong association with thrombosis risk.

**Useful For:** Confirming or excluding the presence of a lupus-like circulating anticoagulant inhibitor (LA), in conjunction with other appropriate coagulation tests Differentiating between deficiencies or inhibitors of specific coagulation factors and LA inhibitors Evaluating a prolonged activated partial thromboplastin time resulting from inhibition

**Interpretation:** The diagnosis of a lupus anticoagulant (LA) requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LAs. Consequently, a combination or panel of coagulation tests are performed, including the activated partial thromboplastin time (APTT) and the dilute Russell viper venom time (DRVVT). If the APTT and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to demonstrate inhibition) and the use of excess phospholipid in appropriate assay systems to confirm the presence of LA. Interpretation of Staclot LA testing is complex, and must be done within the context of several additional laboratory tests (eg, APTT with reflexive APTT mixing study and platelet neutralization procedure: PNP; and DRVVT with reflexive mixing study and confirmatory procedure). The Staclot LA test is based on the comparison between the hexagonal phase phospholipid APTT (Staclot APTT + HEX) and the buffer control APTT (Staclot APTT). Both test specimens include a 1:1 mixture of patient and normal plasma. Plasma containing a LA will demonstrate: 1) a prolonged buffer control APTT (Staclot APTT); 2) a shortened APTT with addition of hexagonal phase phospholipid (Staclot APTT + HEX) relative to the buffer control APTT (Staclot delta). A positive Staclot LA test result is one in which the added hexagonal phase phospholipid (excess phospholipid) shortens the prolonged APTT by at least 8 seconds. The Staclot LA test is highly specific for a LA even in the presence of therapeutic anticoagulation. In evaluation of patient specimens and based on established laboratory procedures and clinical diagnosis, we found that the sensitivity is 96% and the specificity is 88%. However, the overall sensitivity of the Staclot LA test is likely somewhat lower (70%-80%).

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Reference Values:**
Only orderable as part of a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

Staclot delta:
< or =8 seconds

**Clinical References:**

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**STEM 82696**

**Stemphyllium, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Stemphyllium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<td>1</td>
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<tr>
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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
Sterols, Plasma

Clinical Information: Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play an important role in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. Desmosterolosis (desmosterol reductase deficiency) is a very rare disorder of cholesterol biosynthesis with a clinical phenotype similar to that of Smith-Lemli-Opitz (SLO) syndrome (7-dehydrocholesterol reductase deficiency). It is caused by variants in DHCR24 (3-beta-hydroxyysterol delta-24-reductase). To date, less than 20 cases of desmosterolosis have been described. Its biochemical marker is the marked elevation of desmosterol in plasma, tissue, and cultured cells. Another very rare disorder of cholesterol biosynthesis is lathosterolosis caused by variants in SC5DL (sterol 3-beta-hydroxysteroid-delta-5-desaturase). Less than 20 patients have been described to date, but the phenotype appears to be characterized by dysmorphic features, multiple congenital anomalies including those of limb and kidney, intellectual disability, and liver disease. Biochemical abnormalities include elevated lathosterol and transaminases, hyperbilirubinemia, and absent 7-dehydrocholesterol. Sitosterolemia is a rare autosomal recessive disorder caused by variants in the ATP-binding cassette (ABC) transporter genes, ABCG5 and ABCG8, which abnormally enhance the absorption of plant sterols and cholesterol from the intestines. Patients often present with hematologic abnormalities and tendon and tuberous xanthomas as well as premature coronary artery disease. A biochemical diagnosis of sitosterolemia is made by documenting elevations of the plant sterols sitosterol and campesterol in plasma or serum. Cerebrotendinous xanthomatosis (CTX), also known as 27-hydroxylase deficiency, is caused by variants in the CYP27A1 gene. CTX is an autosomal recessive sterol storage disease resulting in the accumulation of cholestanol and cholesterol in most tissues and markedly increased levels of cholestanol in serum. Additionally the ketosterol bile acid precursors (7-alpha-hydroxy-4-cholesten-3-one [7a-C4] and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one [7a12aC4]) are elevated in multiple tissues throughout the body and can be measured in blood or plasma (see CTXBS / Cerebrotendinous Xanthomatosis, Blood Spot; CTXWB / Cerebrotendinous Xanthomatosis, Blood; or CTXP / Cerebrotendinous Xanthomatosis, Plasma). Clinical symptoms, which are variable, develop gradually and can include early chronic diarrhea, followed by bilateral cataracts, tuberous and tendon xanthomas, early atherosclerosis, and progressive neurologic impairment such as ataxia, paraparesis, cerebellar ataxia, and dementia. CTX should be suspected in patients with tendon xanthomas and normal or elevated serum cholesterol, and considered in cases of unexplained juvenile cataracts X-linked chondrodysplasia punctata 2 (CDPX2) and MEND (male EBP disorder with neurologic defects) are caused by defects in EBP, which codes for emopamil binding protein, an important enzyme in the final steps of the sterol biosynthesis pathway. CDPX2 is a typically male-lethal X-linked dominant skeletal dysplasia with accompanying skin, hair, nail, and eye abnormalities (ichthyosis in the newborn, scarring alopecia, cataracts). The phenotype in affected males is variable ranging from severe skeletal and internal anomalies leading to fetal demise or stillbirth to milder short stature or even asymptomatic carriers. MEND syndrome, caused by non-mosaic partial loss of function variants in EBP, affects primarily males. It is a neurologic phenotype characterized by moderate-to-severe developmental delay and central nervous system malformations, in particular Dandy-Walker malformation, agenesis of the corpus callosum, and hydrocephalus. Many patients have dysmorphic features that overlap with Smith-Lemli-Opitz syndrome (2-3 toe syndactyly, postaxial...
polydactyly, and urogenital anomalies). Females are rarely affected. Biochemical abnormalities for CDXP2 and MEND include elevated 8(9)-cholestenol and 8-dehydrocholesterol. Sterol C4 methyl oxidase deficiency (SC4MOL) is an autosomal recessive inborn error of cholesterol metabolism characterized by microcephaly, congenital cataracts, and psoriasiform dermatitis. Other features include immune dysregulation, joint pain, short stature and intellectual disability. Biochemical abnormalities include increased plasma 4,4’-dimethyl and 4alpha-monomethylsterols such as dihydro T-MAS (4,4’-dimethyl-5alpha-cholesta-8(9)-en-3beta-ol), and decreased total, low-density lipoprotein, and high-density lipoprotein cholesterol.

**Useful For:** Investigation of possible desmosterolosis (desmosterol reductase deficiency), cerebrotendinous xanthomatosis, lathosterolosis, sitosterolemia, sterol C4 methyl oxidase deficiency, MEND (male EBP disorder with neurologic defects) syndrome and X-linked chondrodysplasia punctata 2

**Interpretation:** A quantitative report of the patient's sterol profile and a Biochemical Genetics consultant's interpretation is provided for each specimen.

**Reference Values:**

- **7-DEHYDROCHOLESTEROL**
  \(< or = 2.0 \text{ mg/L}\)

- **8-DEHYDROCHOLESTEROL**
  \(< or = 0.3 \text{ mg/L}\)

- **8(9)-CHOLESTENOL**
  \(< or = 5.0 \text{ mg/L}\)

- **CAMPESTEROL**
  \(< or = 8.0 \text{ mg/L}\)

- **CHOLESTANOL**
  \(< or = 6.0 \text{ mg/L}\)

- **DESMOSTEROL**
  \(< or = 2.5 \text{ mg/L}\)

- **DIHYDRO T-MAS**
  \(< or = 0.3 \text{ mg/L}\)

- **LATHOSTEROL**
  \(< or = 6.0 \text{ mg/L}\)

- **SITOSTEROL**
  \(< or = 15.0 \text{ mg/L}\)

- **SQUALENE**
  \(< or = 1.0 \text{ mg/L}\)

- **STIGMASTEROL**
  \(< or = 0.5 \text{ mg/L}\)


Stinging Insects Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to honeybee, yellow jacket, wasp, yellow faced hornet, and white faced hornet venoms Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tr>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

### STK11 Gene, Full Gene Analysis, Varies

**Clinical Information:** Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by gastrointestinal (GI) hamartomatous polyps and melanotic macules. The GI polyps are most common in the small intestine. Although typically benign, these polyps can cause chronic bleeding and may result in obstruction and intussusception. Pigment changes, typically dark blue spots around the lips, buccal mucosa, and fingers, appear in childhood. Affected individuals are also at an increased risk for a variety of malignancies including colorectal, gastric, breast, thyroid, pancreatic, uterine, and sertoli cell and sex cord tumors. PJS is caused by variants in the STK11 (formerly LKB1) gene.

**Useful For:** Confirming a diagnosis of Peutz-Jeghers syndrome

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### Strawberry IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Strawberry, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and...
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to strawberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


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**SABP 86537**

**Streptococcal Antibodies Profile, Serum**

Clinical Information: A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonuclease (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

Useful For: Demonstration of acute or recent streptococcal infection using both antistreptolysin O and anti-DNase B titers

Interpretation: Elevated values are consistent with an antecedent infection by group A streptococci.

Reference Values:

**ANTISTREP-O TITER**

<5 years: < or =70 IU/mL

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5-17 years: ≤ 640 IU/mL
≥ 18 years: ≤ 530 IU/mL

ANTI-DNase B TITER
<5 years: ≤ 250 U/mL
5-17 years: ≤ 375 U/mL
≥ 18 years: ≤ 300 U/mL


SPNEU
Streptococcus pneumoniae Antigen, Random, Urine

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia (CAP). Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are provided for CAP without culture confirmation of S pneumoniae, antigen testing may be useful.

Useful For: Rapid diagnosis of pneumococcal pneumonia

Interpretation: A positive result is indicative of pneumococcal pneumonia. A negative result is a presumptive negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the detection limit of the test.

Reference Values:
Negative


SPNC
Streptococcus pneumoniae Antigen, Spinal Fluid

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia, and can also be an agent of bacterial meningitis. Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are being considered prior to culture confirmation, antigen testing may be useful.

Useful For: Rapid diagnosis of pneumococcal meningitis

Interpretation: A positive result supports a diagnosis of pneumococcal meningitis. A negative result suggests that pneumococcal antigen is absent in the cerebrospinal fluid (CSF). However, infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the lower limit of detection of the test. If pneumococcal meningitis is suspected, bacterial culture and Gram-stain analysis on CSF should be performed.

Reference Values:
Negative

Reference values apply to all ages.

Streptococcus pneumoniae IgG Antibodies, 23 Serotypes, Serum

Clinical Information: Streptococcus pneumoniae is a gram-positive bacteria that causes a variety of infectious diseases in children and adults, including invasive disease (bacteremia and meningitis) and infections of the respiratory tract (pneumonia and otitis media). In 2009, it is estimated that S pneumoniae was responsible for approximately 43,500 infections and 5,000 deaths in the United States. More than 90 serotypes of S pneumoniae have been identified, based on varying polysaccharides that are found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune response. Vaccines containing bacterial polysaccharides can be effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma and memory B cells, which can protect an individual against bacterial disease. Active immunization of adults and children older than 2 years is performed with nonconjugated polysaccharide vaccines (Pneumovax and Pnu-Immune 23) that contain a total of 23 serotypes, namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F.(3) These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Antibody responses develop in approximately 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization. Immunization with a 23-valent vaccine is recommended for all adults 65 years of age and older, and for adults 18 to 64 years of age with certain chronic diseases (heart disease, lung disease, type I diabetes, liver disease), those who are immunocompromised (congenital or acquired immunodeficiencies, malignancy, solid-organ transplant), and those with functional or anatomic asplenia.(3) In contrast to adults and older pediatrics, immune responses to polysaccharide antigens in children younger than 2 years of age are generally weak. Active immunization of children younger than 2 years requires multiple injections of vaccine prepared from purified polysaccharides conjugated to an immunogenic carrier (Corynebacterium diphtheria strain C7 protein), which results in a T-cell dependent antibody response. In children younger than age 6, prior to the availability of routine S pneumoniae vaccination, 7 serotypes (4, 6B, 9V, 18C, 19F, and 23F) accounted for 80% of invasive disease and up to 100% of all isolates that were found to be highly resistant to treatment with penicillin. The first conjugated vaccine available for children younger than age 2 (Prevnar) contained these 7 serotypes.(4,5) The vaccine was highly effective, with invasive disease in children younger than age 5 reduced from 99 to 21 cases per 100,000 population from 1998 to 2008. In addition, it was demonstrated that after Prevnar became part of the routine vaccination schedule, only 2% of invasive disease was associated with any of the serotypes present in the 7-valent conjugate vaccine. Instead, approximately 61% of the invasive disease was caused by an additional 6 serotypes, including 1, 3, 5, 6A, 7F, and 19A. This led to development of a 13-valent S pneumoniae polysaccharide conjugate vaccine, which is marketed as Prevnar13. Prevnar13 is approved for administration to all children ages 6 weeks to 71 months, and has replaced the previous 7-valent Prevnar vaccine.(6) Patients with intrinsic defects in humoral immunity, such as common variable immunodeficiency, may have impaired antibody responses to pneumococcal vaccination. Further, impaired polysaccharide responsiveness, also known as selective antibody deficiency, is a recognized clinical entity in patients older than 2 years and is characterized by recurrent bacterial respiratory infections, absent or subnormal antibody response to a majority of the polysaccharide antigens, and normal or increased immunoglobulin levels, including IgG subclasses, in the context of an intact humoral response to protein antigens. In several other primary immunodeficiencies, including Wiskott-Aldrich syndrome, autoimmune lymphoproliferative syndrome, and DiGeorge syndrome, IgG-subclass deficiencies may also result in impaired antibody responses to polysaccharide antigens.

Useful For: Assessing the IgG antibody response to active immunization with nonconjugated,
23-valent vaccines Assessing the IgG antibody response to active immunization with conjugated, 13-valent vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigens, as part of an evaluation for humoral or combined immunodeficiencies

**Interpretation:** As a general guideline, nonimmunocompromised adults develop IgG antibodies approximately 4 to 6 weeks following nonconjugated vaccination. A study conducted at the Mayo Clinic assessed IgG antibody concentrations prior to and following vaccination in a cohort of 100 healthy adults who met stringent exclusion criteria, including lack of previous pneumococcal vaccination or pneumonia associated with Streptococcus pneumoniae infection. Based on this data, reference ranges were established that most effectively discriminated between prevaccination and postvaccination antibody concentrations. Antibody concentrations greater than or equal to the reference value for at least 50% of serotypes in either a pre- or postvaccination specimen or a 2-fold or greater increase in antibody concentrations for at least 50% of serotypes when comparing the pre- to the postvaccination results would be consistent with a normal response to S pneumoniae vaccination. Serotype-specific antibodies may persist for up to 10 years following immunization or infection.

**Reference Values:**

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<td>&gt; or =1.0</td>
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<tr>
<td>33F (70)</td>
<td>&gt; or =1.7</td>
</tr>
</tbody>
</table>

**Clinical References:**
3. Nuorti JP, Whitney CG: Updated recommendations for prevention of invasive

Streptococcus pneumoniae IgG Antibodies, Total, Serum

Clinical Information: Streptococcus pneumoniae is a gram-positive bacterium that causes a variety of infectious diseases in children and adults. These include invasive disease (bacteremia and meningitis) and infections of the respiratory tract (pneumonia and otitis media). There is an annual estimated number of 5000 cases of pneumococcal bacteremia (without pneumonia) with a fatality rate of approximately 20%, reaching as high as 60% in the elderly population. It is estimated that as many as 400,000 hospitalizations from pneumococcal pneumonia occur annually in the United States, with a case-fatality rate of 5% to 7%. More than 90 serotypes of S pneumoniae have been identified, based on varying polysaccharides that are found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune response. Vaccines containing bacterial polysaccharides can be effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma and memory B cells, which can protect an individual against bacterial disease. Active immunization is performed with a nonconjugated polysaccharide vaccine (Pneumovax) that contains a total of 23 serotypes, namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. These 23 serotypes were included because as a group, they account for approximately 90% of invasive pneumococcal infections. This nonconjugated vaccine is indicated for all adults 65 years of age and older, individuals between 2 and 64 years with chronic diseases (heart disease, lung disease, type I diabetes, liver disease), those who are immunocompromised (congenital or acquired immunodeficiencies, malignancy, solid-organ transplant), those with functional or anatomic asplenia, and adults 19 to 64 years who smoke. Because not all patients can generate a robust T-cell independent antibody response, conjugated vaccines such as Prevnar (7-valent) and Prevnar 13 (13-valent) were developed, in which the polysaccharide is conjugated to the CRM197 protein and therefore initiates a T-cell dependent antibody response. Immunization with the conjugated vaccine is indicated in all children under 2 years old, all adults 65 years and older, and individuals with medical conditions such as immunodeficiency, chronic obstructive pulmonary disease, and congestive heart failure. Antibody responses develop in approximately 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization.

Useful For: Assessing the IgG antibody response to active immunization with nonconjugated 23-valent vaccines Assessing the IgG antibody response to active immunization with conjugated 13-valent and 7-valent vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigens, as part of an evaluation for humoral or combined immunodeficiencies

Interpretation: Low anti-pneumococcal antibody concentrations (<9.7 mcg/mL) indicate a poor response to the pneumococcal vaccine, while high concentrations (>270.0 mcg/mL) indicate a robust vaccine response. Results falling in the modest (9.7-40.9 mcg/mL), intermediate (41.0-180.9 mcg/mL), and moderate (181.0-270.0 mcg/mL) categories may warrant serotype-specific antibody testing, to be determined at the discretion of the physician. When comparing pre- and post-vaccination samples, an
increase in antibody concentrations is generally considered to be indicative of a normal vaccine response. However, the specific fold increase is influenced substantially by the antibody concentration observed in the pre-vaccination sample.

**Reference Values:**

> or ≥ 9.7 mcg/mL

**Clinical References:**


**Streptococcus pneumoniae IgG Antibodies, Total, with Reflex, Serum**

**Clinical Information:** Streptococcus pneumoniae is a gram-positive bacterium that causes a variety of infectious diseases in children and adults. These include invasive disease (bacteremia and meningitis) and infections of the respiratory tract (pneumonia and otitis media). There is an annual estimated number of 5000 cases of pneumococcal bacteremia (without pneumonia) with a fatality rate of approximately 20%, reaching as high as 60% in the elderly population. It is estimated that as many as 400,000 hospitalizations from pneumococcal pneumonia occur annually in the United States, with a case-fatality rate of 5% to 7%. More than 90 serotypes of S pneumoniae have been identified, based on varying polysaccharides that are found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune response. Vaccines containing bacterial polysaccharides can be effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma and memory B cells, which can protect an individual against bacterial disease. Active immunization is performed with a nonconjugated polysaccharide vaccine (Pneumovax) that contains a total of 23 serotypes, namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. This nonconjugated vaccine is indicated for all adults 65 years of age and older, individuals between 2 and 64 years with chronic diseases (heart disease, lung disease, type I diabetes, liver disease), those who are immunocompromised (congenital or acquired immunodeficiencies, malignancy, solid-organ transplant), those with functional or anatomic asplenia, and adults 19 to 64 years who smoke. Because not all patients can generate a robust T-cell independent antibody response, conjugated vaccines such as Prevnar (7-valent) and Prevnar 13 (13-valent) were developed, in which the polysaccharide is conjugated to the CRM197 protein and therefore initiates a T-cell dependent antibody response. Immunization with the conjugated vaccine is indicated in all children under 2 years old, all adults 65 years and older, and individuals with medical conditions such as immunodeficiency, chronic obstructive pulmonary disease, and congestive heart failure. Antibody responses develop in approximately 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization.

**Useful For:** Assessing the IgG antibody response to active immunization with nonconjugated 23-valent vaccines Assessing the IgG antibody response to active immunization with conjugated 13-valent and 7-valent vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigens, as part of an evaluation for humoral or combined immunodeficiencies

**Interpretation:** Low antipneumococcal antibody concentrations (< 9.7 mcg/mL) indicate a poor
response to the pneumococcal vaccine, while high concentrations (>270.0 mcg/mL) indicate a robust vaccine response. Results falling in the modest (9.7-40.9 mcg/mL), intermediate (41.0-180.9 mcg/mL), and moderate (181.0-270.0 mcg/mL) categories may warrant serotype-specific antibody testing, to be determined at the discretion of the physician. When comparing pre- and post-vaccination samples, an increase in antibody concentrations is generally considered to be indicative of a normal vaccine response. However, the specific fold increase is influenced substantially by the antibody concentration observed in the pre-vaccination sample.

**Reference Values:**
> or =9.7 mcg/mL

**Clinical References:**

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**Strict Criteria Sperm Morphology for Infertility Diagnosis and Treatment, Semen**

**Clinical Information:** Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Abnormalities in sperm morphology are related to: defects in sperm transport, sperm capacitation, the acrosome reaction, binding/penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple's IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).

**Useful For:** Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

**Interpretation:** Categorizing sperm according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

**Reference Values:**

- Normal forms
  - > or =4.0%
  - Germinal cells/mL
  - <4 x 10(6) (normal)
  - > or =4 x 10(6) (Elevated germinal cells in semen are of unknown clinical significance)
  - WBC/mL
  - <1 x 10(6) (normal)
  - > or =1 x 10(6) (Elevated white blood cells in semen are of questionable clinical significance)

STRICTSperm

Strict Criteria Sperm Morphology for Infertility Diagnosis and Treatment, Semen

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Useful For: Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

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Reference Values:
Normal forms: > or =4.0%
Germinial cells/mL
<4 x 10(6) (normal)
> or =4 x 10(6) (elevated germinal cells in semen are of unknown clinical significance)
WBC/mL
<1 x 10(6) (normal)
> or =1 x 10(6) (elevated white blood cells in semen are of questionable clinical significance)

Clinical References: Kruger Morphology Conference, Boston, MA, October 9, 1993

STRONGELlodyoides Antibody, IgG, Serum

Clinical Information: Strongyloidiasis is caused by Strongyloides stercoralis, a nematode endemic to tropical and subtropical regions worldwide. S. stercoralis is also prominent in the southeastern United States, including in rural areas of Kentucky, Tennessee, Virginia, and North Carolina. A small series of epidemiological studies in the United States identified that 0% to 6.1% of individuals sampled had antibodies to S. stercoralis. S. stercoralis has a complex lifecycle that begins with maturation to the infective filariform larva in warm, moist soil. The larvae subsequently penetrate exposed skin and migrate hematogenously to the lungs, from where they ascend the bronchial tree and are swallowed. Once in the small intestine, filariform larva matures into the adult worms that burrow into the mucosa. Gravid female worms produce eggs that develop into noninfectious rhabditiform larvae in the gastrointestinal tract and are eventually released in the stool. The time from dermal penetration to appearance of Strongyloides in stool samples is approximately 3 to 4 weeks. The most common manifestations of infection are mild and may include epigastric pain, mild diarrhea, nausea, and vomiting. At the site of filariform penetration, skin may be inflamed and itchy-this is referred to as "ground itch." Migration of the larva through the lungs and up the trachea can produce a dry cough, wheezing, and mild hemoptysis. Eosinophilia, though common among patients with strongyloidiasis, is not a universal finding and the absence of eosinophilia cannot be used to rule-out infection. In some patients, particularly those with a depressed immune system, the rhabditiform larvae may mature into the infectious filariform larvae in the gastrointestinal tract and...
lead to autoinfection. The filariform larvae subsequently penetrate the gastrointestinal mucosa, migrate to the lungs, and can complete their lifecycle. Low-level autoinfection can maintain the nematode in the host for years to decades. Among patients who become severely immunocompromised, however, autoinfection may lead to hyperinfection and fatal disseminated disease. Hyperinfection has also been associated with underlying human T-cell lymphotropic virus type 1 (HTLV-1) infection. Uncontrolled, the larvae can disseminate to the lungs, heart, liver, and central nervous system. Septicemia and meningitis are common in cases of Strongyloides hyperinfection due to seeding of the bloodstream and central nervous system with bacteria originating from the gastrointestinal tract.

**Useful For:** Screening for the presence of IgG-class antibodies to Strongyloides This test is not useful for monitoring patient response to therapy as IgG-class antibodies to Strongyloides may remain detectable following resolution of infection.

**Interpretation:** Positive: IgG antibodies to Strongyloides were detected, suggesting current or past infection. False-positive results may occur with other helminth infections (eg, Trichinella, Taenia solium). Clinical correlation is required. Negative: No detectable levels of IgG antibodies to Strongyloides. Repeat testing in 10 to 14 days if clinically indicated.

**Reference Values:**
- **Negative**
  - Reference values apply to all ages.

**Clinical References:**

**FSTYR**

**Styrene, Occupational Exposure, Blood**

**Reference Values:**
- **Normal (Unexposed population):**
  - None detected

- **Exposed:**
  - Biological Exposure Index (BEI):
    - 0.55 mg/L (end of shift)
    - 0.02 mg/L (prior to next shift)

- **Toxic:**
  - Not established

**SUBS**

**Subseq Antib MIC (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**SUAC**

**Succinylacetone, Blood Spot**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Clinical Information:** Tyrosinemia type 1 (hepatorenal tyrosinemia, HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). HT-1 primarily affects the liver, kidneys, and peripheral nerves causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma. Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanone (NTBC) is available and is particularly effective when initiated in newborns. The incidence of HT-1 is approximately 1 in 100,000 live births. While tyrosine can be determined by routine newborn screening, it is not a specific marker for tyrosinemia type I and often may be associated with common and benign transient tyrosinemia of the newborn. Succinylacetone (SUAC) is a specific marker for HT-1, but not consistently measured by newborn screening programs. This assay determines succinylacetone and tyrosine in newborn blood spots by tandem mass spectrometry. Additional follow-up testing may include confirmatory molecular analysis of the FAH gene.

**Useful For:** Second-tier newborn screen for tyrosinemia type 1 (HT-1) when primary screen showed nonspecific elevations of tyrosine Diagnosis of HT-1 when used in conjunction with testing for urine organic acids (OAU), liver function tests, alpha-fetoprotein, and molecular genetic analysis of FAH

**Interpretation:** Elevations of succinylacetone (SUAC) above the reference range with or without elevations of tyrosine (TYR) are indicative of tyrosinemia type 1. Elevations of TYR above the reference range without elevations of SUAC may be suggestive of tyrosinemia type II, type III, transient hypertyrosinemia of the neonate, or nonspecific liver disease.

**Reference Values:**

**Succinylacetone**

<1.00 nmol/mL

**Tyrosine**

<4 weeks: 40.0-280.0 nmol/mL
> or =4 weeks: 25.0-150.0 nmol/mL


**FSUCC 57460**

Succinyladenosine, CSF

**Reference Values:**

Reference Range: 0.74 Å€Å—â€œ to 4.92 umol/L

**SUDC 606930**

Sudden Cardiac Death Pathology Consultation

**Clinical Information:** Sudden, unexpected death in individuals less than 40 years old with a strong probability of cardiac disease (including cases of obvious cardiomyopathy, with likely genetic underpinning). This evaluation is offered to provide the careful dissection and diagnostic experience that may be needed for subtle or overt cases of cardiovascular disease.

**Useful For:** Identifying specific causes contributing to sudden cardiac death

**Interpretation:** This request will be processed as a consultation. Appropriate stains and ancillary testing will be performed and an interpretation provided.
Reference Values:
The laboratory will provide a pathology consultation.


Sugar Cane (Saccharum officinarum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35  0.69 Low Positive 2 0.70  3.49 Moderate Positive 3 3.50  17.49 Positive 4 17.50  49.99 Strong Positive 5 50.00  99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

Sugarbeet Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to sugar beet seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Interpretation</th>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
</tbody>
</table>
SFZ 8238

Sulfamethoxazole, Serum

Clinical Information: Sulfamethoxazole is a sulfonamide antibiotic that is administered in conjunction with another antibacterial, trimethoprim. These agents are used to treat a variety of infections including methicillin-resistant Staphylococcus aureus and for prophylaxis in immunosuppressed patients, such as HIV-positive individuals. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Monitoring of sulfamethoxazole is indicated only when prolonged (>3 months) therapy is required. Sulfamethoxazole is absorbed readily after oral administration, with peak serum concentration occurring 2 to 3 hours after an oral dose. Its average elimination half-life is 6 to 10 hours. Toxicity includes crystalluria with resultant calculi and renal disease. Toxicity is due to a high concentration of acetylated, relatively insoluble forms of the drug. Excess fluid should be taken with sulfamethoxazole to avoid formation of urine sulfonamide crystals.

Useful For: Monitoring therapy to ensure drug absorption, clearance, or compliance

Interpretation: Serum drug concentrations should be interpreted with respect to the minimum inhibitory concentration (MIC) of targeted organisms. Most patients will display peak steady-state serum concentrations greater than 50 mcg/mL when collected at least 1 hour after an oral dose. Targets concentrations may be higher, depending on the intent of therapy. For Pneumocystis carinii pneumonia (PCP pneumonia), peak concentrations: 100-150 mcg/mL Toxicity: >200 mcg/mL Toxicity (formation of urinary crystals) associated with sulfamethoxazole occurs with prolonged exposure to serum concentrations greater than 125 mcg/mL.

Reference Values:
>50 mcg/mL


SULFU 606479

Sulfate, 24 Hour, Urine

Clinical Information: Urinary sulfate is a reflection of dietary protein intake, particularly meat, fish, and poultry, which are rich in sulfur-containing amino acids methionine and cysteine. Urinary sulfate can be used to assess dietary protein intake for nutritional purposes. A protein-rich diet has been associated with an increased risk for stone formation, possibly due, in part, to an increase in urinary calcium excretion caused by acid production from metabolism of sulfur-containing amino acids.(1,2) Indeed,
urinary sulfate excretion is higher in patients who have kidney stones than in individuals who do not form stones. Thus, urinary sulfate excretion may provide an index for protein-induced calciuria. Sulfate is a major anion in the urine that has significant affinity for cations and modulates the availability of cations for reacting with other anions in the urine. It thus is an important factor of urinary supersaturation for various crystals or stones such as calcium oxalate, hydroxyapatite, and brushite. For example, a high sulfate concentration may modulate the availability of calcium for reacting with oxalate and thus affect the propensity for calcium oxalate stone or crystal formation. Urinary sulfate also has a major impact on buffering or providing hydrogen ions and as such modulates the supersaturation of uric acid.

**Useful For:** Assessing the nutrition intake of animal protein The calculation of urinary supersaturation of various crystals or stones

**Interpretation:** Urinary sulfate is a reflection of dietary protein intake, particularly of meat, and thus can be used as an index of nutritional protein intake. It also is used in the calculation of urinary supersaturation of various crystals or stones.

**Reference Values:**
7-47 mmol/24 hours

**Clinical References:**

**Sulfatide Autoantibody Test**

**Clinical Information:** Background information: Peripheral neuropathies (PNs) are a group of neurological disorders affecting one or more of the peripheral nerves (1,2). Causes of PN include nerve compression, genetic mutations, inflammation, metabolic abnormalities, vitamin deficiencies, exposure to toxins or drugs, or the presence of autoimmune antibodies (1). Symptoms of PN vary based on location and mechanism of nerve damage but can include sensory impairment, distal weakness, loss of sensation, muscle weakness, and pain (1,2). PNs are typically classified based on the types of nerves affected, predominantly motor, predominantly sensory, or a combination of both (2). IgG and more commonly IgM Antibodies to sulfatide have been associated with sensory and sensory-motor neuropathies sometimes accompanied by pain (3,4,5). Additionally, IgG anti-sulfatide antibodies have been associated with distal sensory polyneuropathy (DSP) in individuals with HIV (6).

**Reference Values:**
A final report will be attached in MayoAccess.

**Clinical References:**

**Sulfonylurea Screen, Urine**

**Reference Values:**
Reference Range: Not Established

Acetohexamide, UR ug/mL
Sunflower Seed IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Sunflower Seed, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to sunflower seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
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</tbody>
</table>
Sunflower, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to sunflower Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Supersaturation Profile, 24 Hour, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (e.g., citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (e.g., calcium oxalate). Since the supersaturation of urine has been shown to correlate with stone type, therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

Useful For: Diagnosis and management of patients with renal lithiasis: Predicting the likely composition of the stone, in patients who have a radiopaque stone, for whom stone analysis is not available. This may help in designing a treatment program. Aiding in identification of specific risk factors for stones using a 24-hour urine collection Monitoring the effectiveness of therapy by confirming that the crystallization potential has indeed decreased Evaluation of kidney excretion of acid and urine pH Estimation of a patient’s protein intake

Interpretation: Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive, even in normal individuals, but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of non-stone formers, on average, the DG is even more positive in those individuals who do form kidney stones. The reference values were simply derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of non-stone formers. Those DG values that are outside the expected range in a population of non-stone formers are marked abnormal. If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (e.g., diarrhea or malabsorption), or an exogenous acid load (e.g., excessive consumption of meat protein). A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (i.e., primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. Low urine ammonium and high urine pH suggest renal tubular acidosis. Such patients are at risk of calcium phosphate stones. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base), this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. The protein catabolic rate is calculated from urine urea. Under routine conditions, the required protein intake is often estimated as 0.8 g/kg body weight. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load), which promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: Calcium oxalate stones: urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention.
phosphate stones (apatite or brushite): urinary volume, calcium, pH, and citrate significantly influence the supersaturation for calcium phosphate. Of note, a urine pH of less than 6 may help reduce the tendency for these stones to form. -Uric acid stones: urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is greater than 6. -Sodium urate stones: alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones.

**Reference Values:**

**SUPERSATURATION REFERENCE MEANS (Delta G: DG)**
- Calcium oxalate: 1.77 DG
- Brushite: 0.21 DG
- Hydroxyapatite: 3.96 DG
- Uric acid: 1.04 DG
- Sodium urate: 1.76 DG

**INDIVIDUAL URINE ANALYTES**

**OSMOLALITY**
- 0-11 months: 50-750 mOsm/kg
- > or =12 months: 150-1,150 mOsm/kg

**pH**
- 4.5-8.0

**ALL REFERENCE RANGES BELOW ARE BASED ON 24-HOUR COLLECTIONS.**

**SODIUM**
- > or =18 years: 22-328 mmol/24h
Reference values have not been established for patients who are less than 18 years of age.

**POTASSIUM**
- > or =18 years: 16-105 mmol/24h
Reference values have not been established for patients who are less than 18 years of age.

**CALCIUM**
- Males: <250 mg/24 hours
- Females: <200 mg/24 hours
Reference values have not been established for patients who are less than 18 years of age.

**MAGNESIUM**
- > or =18 years: 51-269 mg/24 hours
Reference values have not been established for patients who are less than 18 years of age.

**CHLORIDE**
- > or =18 years: 34-286 mmol/24h
Reference values have not been established for patients who are less than 18 years of age.

**PHOSPHORUS**
- > or =18 years: 226-1,797 mg/24 hours
Reference values have not been established for patients who are less than 18 years of age.

**SULFATE**
- 7-47 mmol/24 hours

**CITRATE EXCRETION**
- 0-19 years: not established
- 20 years: 150-1,191 mg/24 hours
- 21 years: 157-1,191 mg/24 hours
22 years: 164-1,191 mg/24 hours
23 years: 171-1,191 mg/24 hours
24 years: 178-1,191 mg/24 hours
25 years: 186-1,191 mg/24 hours
26 years: 193-1,191 mg/24 hours
27 years: 200-1,191 mg/24 hours
28 years: 207-1,191 mg/24 hours
29 years: 214-1,191 mg/24 hours
30 years: 221-1,191 mg/24 hours
31 years: 228-1,191 mg/24 hours
32 years: 235-1,191 mg/24 hours
33 years: 242-1,191 mg/24 hours
34 years: 250-1,191 mg/24 hours
35 years: 257-1,191 mg/24 hours
36 years: 264-1,191 mg/24 hours
37 years: 271-1,191 mg/24 hours
38 years: 278-1,191 mg/24 hours
39 years: 285-1,191 mg/24 hours
40 years: 292-1,191 mg/24 hours
41 years: 299-1,191 mg/24 hours
42 years: 306-1,191 mg/24 hours
43 years: 314-1,191 mg/24 hours
44 years: 321-1,191 mg/24 hours
45 years: 328-1,191 mg/24 hours
46 years: 335-1,191 mg/24 hours
47 years: 342-1,191 mg/24 hours
48 years: 349-1,191 mg/24 hours
49 years: 356-1,191 mg/24 hours
50 years: 363-1,191 mg/24 hours
51 years: 370-1,191 mg/24 hours
52 years: 378-1,191 mg/24 hours
53 years: 385-1,191 mg/24 hours
54 years: 392-1,191 mg/24 hours
55 years: 399-1,191 mg/24 hours
56 years: 406-1,191 mg/24 hours
57 years: 413-1,191 mg/24 hours
58 years: 420-1,191 mg/24 hours
59 years: 427-1,191 mg/24 hours
60 years: 434-1,191 mg/24 hours
>60 years: not established

OXALATE
0.11-0.46 mmol/24 hours
9.7-40.5 mg/24 h

URIC ACID
Male: > or =18 years: 200-1,000 mg/24h
Female: > or =18 years: 250-750 mg/24h
Reference values have not been established for patients who are less than 18 years of age.

CREATININE
Male: > or =18 years: 930-2,955 mg/24h
Female: > or =18 years: 603-1,783 mg/24h
Reference values have not been established for patients who are less than 18 years of age.

AMMONIUM
15-56 mmol/24 hour
Reference values have not been established for patients <18 years and >77 years of age.

**UREA NITROGEN**

> or =18 years: 7-42 g/24h

Reference values have not been established for patients who are less than 18 years of age.

**PROTEIN CATABOLIC RATE**

56-125 g/24 hours

**Clinical References:**

**SSATR 36907**

**Supersaturation Profile, Random, Urine**

**Clinical Information:** Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

**Useful For:** Diagnosis and management of patients with renal lithiasis: -Predicting the likely composition of the stone, in patients who have a radiopaque stone, for whom stone analysis is not available. This may help in designing a treatment program -Identifying specific risk factors for stones formation using a random urine collection -Monitoring the effectiveness of therapy by confirming that the crystallization potential has indeed decreased -Evaluation of kidney excretion of acid and urine pH

**Interpretation:** Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive, even in normal individuals, but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of non-stone formers, on average, the DG is even more positive in those individuals who do form kidney stones. The reference values are simply derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of non-stone formers. Those DG values that are outside the expected range in a population of non-stone formers are marked abnormal. A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg, excessive consumption of meat protein). An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium
phosphate stones. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load), which promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: Urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): Urine volume, calcium, pH, and citrate significantly influence the supersaturation for calcium phosphate. Of note, a urine pH of less than 6 may help reduce the tendency for these stones to form. -Uric acid stones: Urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is greater than 6. -Sodium urate stones: Alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones. The following reference means for calculated supersaturation apply to 24-hour timed collections. No information is available for random collections. Supersaturation Reference Means (ΔG: DG) Brushite: 0.21 DG Hydroxyapatite: 3.96 DG Uric acid: 1.04 DG Sodium urate: 1.76 DG Values for individual analytes that are part of this panel on a random urine collection are best interpreted as a ratio to the creatinine excretion. Following are pediatric reference ranges for which pediatric data is available. Oxalate/creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048 Matos V, Van Melle G, Werner D, et al: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999;34:81 Uric Acid/creatinine (mg/mg) Age (year) 5th Percentile 0.5-1 >1.189 >0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594 Matos V, Van Melle G, Werner D, et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997;131:252-257 Magnesium/creatinine (mg/g) Age (year) 95th Percentile <0.86 0-1 <0.33 1-2 <0.32 2-3 <0.29 3-5 <0.21 5-7 <0.18 7-10 <0.15 10-14 <0.13 Matos V, van Melle G, Boulat O, et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997;131:252-257 Citrate/creatinine (mg/mg) Age (year) 95th Percentile <1.311 Srivastava T, Winston MJ, Auron A, et al: Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res. 2009;66:85-90

Reference Values:

pH: 4.5-8.0

OSMOLALITY

0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

AMMONIUM

18-77 years: 3-65 mmol/L
No reference values established for <18 years and >77 years of age

CALCIUM

1 month-<12 months: 0.03-0.81 mg/mg creat
12 months-<24 months: 0.03-0.56 mg/mg creat
24 months-<3 years: 0.02-0.50 mg/mg creat
3 years-<5 years: 0.02-0.41 mg/mg creat
5 years-<7 years: 0.01-0.30 mg/mg creat
7 years-<10 years: 0.01-0.25 mg/mg creat
10 years-<18 years: 0.01-0.24 mg/mg creat
18 years-83 years: 0.05-0.27 mg/mg creat
Reference values have not been established for patients who are <1 month of age.
Reference values have not been established for patients who are >83 years of age.

**MAGNESIUM**

*Magnesium/Creatinine Ratio:*

- 1 month→12 months: 0.10-0.48 mg/mg creat
- 12 months→24 months: 0.09-0.37 mg/mg creat
- 24 months→3 years: 0.07-0.34 mg/mg creat
- 3 years→5 years: 0.07-0.29 mg/mg creat
- 5 years→7 years: 0.06-0.21 mg/mg creat
- 7 years→10 years: 0.05-0.18 mg/mg creat
- 10 years→14 years: 0.05-0.15 mg/mg creat
- 14 years→18 years: 0.05-0.13 mg/mg creat
- 18 years→83 years: 0.04-0.12 mg/mg creat

Reference values have not been established for patients who are less than 1 month of age.

Reference values have not been established for patients who are greater than 83 years of age.

**Clinical References:**


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**SNS 82594**

**Supplemental Newborn Screen, Blood Spot**

**Clinical Information:**
Newborn screening as a public health measure was initiated in the early 1960s for the identification of infants affected with phenylketonuria (PKU). Since then, additional genetic and nongenetic conditions were included in state screening programs. The goal of newborn screening is to detect diagnostic markers of the selected disorders in blood spots collected from presymptomatic newborns. Inherited disorders of amino acid, fatty acid, and organic acid metabolism typically manifest during the first 2 years of life as acute metabolic crises and usually result in severe neurologic impairment or death. These metabolic decompensations are usually triggered by intermittent febrile illness, such as common viral infections leading to prolonged fasting and increased energy demands. Early identification of affected newborns allows for early initiation of treatment to avoid mortality, morbidity, and disabilities due to these disorders. Tandem mass spectrometry (MS/MS) is a powerful multianalyte screening method, which is ideally suited for population-wide testing. Since the early 1990s, MS/MS has made screening possible for more than 30 genetic disorders affecting the metabolism of amino acids, fatty acids, and organic acids based on the profiling of amino acids and acylcarnitines in blood spots. The simultaneous MS/MS analysis of amino acids, acylcarnitines, and succinylacetone in dried blood spots can be performed in less than 3 minutes per specimen, generating metabolite profiles that allow for the biochemical diagnosis of multiple disorders. This is in contrast to conventional screening techniques traditionally based on the principle of 1 separate test for each disorder. In Mayo's experience, the combined incidence of the disorders identifiable by MS/MS in a single blood spot analysis is approximately 1 in 1,700 newborns. Supplemental newborn screening by MS/MS as described here does not replace current state screening programs, because MS/MS does not allow primary screening for galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia (CAH), cystic fibrosis, biotinidase, sickle cell disease, Mucopolysaccharidosis type II, Adrenoleukodystrophy, Pompe disease, severe combined immune deficiency (SCID), critical congenital heart disease, and congenital hearing loss. The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) recommends all programs screen for 34 core disorders. These conditions are considered to fulfill 3 basic principles: -Condition is identifiable at a period of time (24-48 hours after birth) at which it would not ordinarily be clinically detected. -Test with appropriate sensitivity and specificity is available. -Demonstrated benefits of early detection, timely intervention, and efficacious treatment. *This test does not screen for critical congenital heart disease and congenital
hearing loss, both of which are tested in the nursery using methods other than blood spots (audiometry, pulse oximetry). Screening tests do not conclusively determine disease status, but measure analytes which in most cases are not specific for a particular disease. This is the reason why the HHS Secretary also recognizes more than 25 additional conditions as secondary targets that do not meet all inclusion criteria but are identified nevertheless because most of them are components of the differential diagnosis of screening results observed in core conditions. Even for the secondary conditions, the possibility of making a diagnosis early in life not only helps avoid unnecessary diagnostic testing, but is also beneficial to the patient's families because genetic counseling and prenatal diagnosis can be offered. Although not currently in the recommended uniform screening panel, guanidinoacetate methyltransferase (GAMT), a disorder of creatine synthesis, is a condition included in the Mayo Clinic Laboratories’ supplemental newborn screen. When untreated, this disorder results in a depletion of cerebral creatine leading to global developmental delays, intellectual disability, severe speech delays, and seizures. Patients with GAMT exhibit behavioral problems and features of autism. Treatment consists of lifelong supplementation with creatine monohydrate, ornithine, and dietary protein restriction to decrease cerebral GAA levels. Individuals with GAMT who are treated before the appearance of symptoms may exhibit normal neurodevelopmental outcomes.

Useful For: Presymptomatic identification of disorders to allow for early initiation of treatment and consequent improvement in the long-term prognosis of affected patients. The conditions identifiable by amino acid and acylcarnitine analysis are detected by supplemental newborn screening using tandem mass spectrometry (MS/MS) as described here. Analyte (assay platform) ACMG Recommended Conditions Additional Conditions/Treatment Detectable by MS/MS Core Condition Secondary Targets Amino Acids (MS/MS) Phe PKU BS HPA REG TPN Leu/Ile, Val MSUD TPN Met HCY Met TPN, nonspecific liver disease Cit, Arg, ASA ASA CIT ARG CIT-II Tyr TYR-I TYR-II TYR-III Nonspecific liver disease GUAC GAMT Acylcarnitines (MS/MS) C0 CUD Maternal CUD, maternal GA-I, maternal MCAD C3 CblA, Cbl B MUT PA Cbl C, Cbl D C4 IBDH SCAD FIGLU C5 IVA SBCAD Antibiotics containing pivalic acid C5-OH BKT HMG MCC MCD MGA-I MBHD Maternal MCC, biotinidase deficiency C8 MCAD1 GA-II1 MCKAT1 M/SCHAD1 C3-DC MAL C10:2 DR C5-DC GA-I C14:1, C16, C18:1 VLCAD CACT CPT-I2 CPT-II C16-OH LCHAD2 TFP2 m/z 225<399<473 Dextrose infusion m/z 342 (C8:1) Artifact often observed in premature neonates m/z 470 (C16:1OH) Cefotaxime metabolite Succinylacetone TYR-I

Interpretation: The quantitative measurements of the various amino acids, acylcarnitines, and succinylacetone support the interpretation of the complete profile but for the most part are not diagnostic by themselves. The interpretation is by pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics. The reports are in text form only, values for the more than 60 analytes and analyte ratios are not provided. A report for a normal screening result is reported as: "In this blood spot sample, the amino acid and acylcarnitine profiles by tandem mass spectrometry showed no biochemical evidence indicative of an underlying metabolic disorder." A report for an abnormal screening result includes a quantitative result of the abnormal metabolites, a detailed interpretation of the results, including an overview of the results significance, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), and a phone number for a contact at Mayo Clinic if the referring physician has additional questions.

Reference Values: An interpretive report will be provided.

newborn screening results without analyte cutoff values. Genet Med 2012;14:648-655

STPPC
Surgical Pathology Touch Prep (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

STAPC
Surgical Pathology Touch Prep Additional (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

SUS
Susceptibility (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

RSLG
Susceptibility Slow Grower (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

STV1
Susceptibility, Mtb Complex, Broth (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

STVP
Susceptibility, Mtb Complex, PZA (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

STV2
Susceptibility, Mtb Cx, 2nd Line (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.
Susceptibility, Mycobacterium tuberculosis Complex, Pyrazinamide, Varies

**Clinical Information:** Primary treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide (PZA). Susceptibility testing of each Mycobacterium tuberculosis complex isolate against these first-line antimycobacterial agents is a key component of patient management. The Clinical and Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility test results. Current recommendations indicate that laboratories should use a rapid broth method in order to obtain Mycobacterium tuberculosis complex susceptibility data as quickly as possible to help guide patient management. According to the CLSI, resistance can be confirmed by another method or by another laboratory at the discretion of the testing laboratory. This test uses an FDA-cleared commercial system for rapid broth susceptibility testing of Mycobacterium tuberculosis complex against PZA. Since the literature indicates that broth testing of PZA can, at times, produce falsely resistant results, resistance to PZA by the broth method is automatically confirmed by pncA DNA sequencing. The pncA gene of Mycobacterium tuberculosis complex is responsible for activation of the prodrug PZA and hence PZA activity. Mutations in the pncA gene and upstream promoter region have been reported to account for the majority (70%-97%) of PZA-resistant isolates. However, 3% to 30% of PZA-resistant isolates do not have a corresponding pncA mutation and other genes (eg, rpsA) may also play a role. A separate test is available for testing of the other first-line agents (isoniazid, rifampin and ethambutol).

**Useful For:** Susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture against pyrazinamide Confirming Mycobacterium tuberculosis complex resistance to pyrazinamide

**Interpretation:** Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to pyrazinamide at the critical concentration.

**Reference Values:**
Results are reported as susceptible or resistant.

**Clinical References:**
**Susceptibility, Mycobacterium tuberculosis Complex, Second Line, Varies**

**Clinical Information:** The Clinical and Laboratory Standards Institute (CLSI) provides a consensus protocol for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility testing results. CLSI guidelines suggest that second-line agents should be tested when an isolate of Mycobacterium tuberculosis complex is resistant to rifampin, is monoresistant to the critical concentration of isoniazid and the physician intends to use a fluoroquinolone for therapy, or is resistant to any combination of 2 first-line agents. This test uses a broth microdilution method for susceptibility testing of Mycobacterium tuberculosis complex against second-line agents. Agents tested are amikacin, cycloserine, ethionamide, kanamycin, moxifloxacin, ofloxacin, p-aminosalicylic acid, rifabutin, and streptomycin. In contrast to other Mycobacterium tuberculosis susceptibility methods which test 1 or 2 critical concentrations of a drug, this method examines a range of drug concentrations and produces an minimal inhibitory concentration result.

**Useful For:** Determination of Mycobacterium tuberculosis complex minimal inhibitory concentrations to second-line antimicrobial agents

**Interpretation:** Results are reported as minimal inhibitory concentrations (MIC) in mcg/mL and tentative interpretations of susceptible or resistant are provided. Agent MIC Range Tested (mcg/mL)

<table>
<thead>
<tr>
<th>MIC Tentative Interpretations (mcg/mL)</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin 0.12-16 or =4.0 &gt;4.0</td>
<td></td>
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</tr>
<tr>
<td>Cycloserine 2-256 or =32.0 &gt;32.0 Ethionamide 0.3-40 or =5.0 &gt;5.0 Kanamycin 0.6-40 or =5.0 &gt;5.0 Moxifloxacin 0.06-8 or =2.0 &gt;2.0 Ofloxacin 0.25-32 or =2.0 &gt;2.0 Para-aminosalicylic acid 0.5-64 or =2.0 &gt;2.0 Rifabutin 0.12-16 or =0.5 &gt;0.5 Streptomycin 0.25-32 or =2.0 &gt;2.0 Isoniazid* 0.03-4 or =0.25 &gt;0.25 Ethambutol* 0.5-32 or =4 &gt;4 Rifampin* 0.12-16 or =1 &gt;1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory-derived tentative interpretations based on MIC breakpoints established relative to the indirect agar proportion method; consensus breakpoint interpretations are not available at this time. (Hall L, Jude KP, Clark SL, et al: Evaluation of the Sensititre MycoTB plate for susceptibility testing of the Mycobacterium tuberculosis complex against first- and second-line agents. J Clin Microbiol 2012;50:3732-3734) *This test is used as an alternative to TB1LN / Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line when reagents are not available to perform the TB1LN test.

**Reference Values:**
Results are reported as minimal inhibitory concentration (MIC) values with units of mcg/mL and tentative interpretations of susceptible or resistant are provided.


---

**Sweet Gum, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and...
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to sweet gum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Sweet Vernal Grass, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to sweet vernal grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
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</tr>
</thead>
<tbody>
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<td>4</td>
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<td>Strongly positive</td>
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**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to swordfish Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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</thead>
<tbody>
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<tr>
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<tr>
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<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Synaptophysin (SYNAPTO) Immunostain, Technical Component Only

Clinical Information: Synaptophysin is a calcium-binding protein present in the presynaptic vesicles of neurons as well as vesicles in the neuroendocrine cells. Synaptophysin is expressed in neuronal tumors and tumors with neuroendocrine differentiation including neuroblastoma, ganglioneuroblastoma, ganglioneuroma, pheochromocytoma/paraganglioma and carcinoid/neuroendocrine carcinoma. Antibodies to synaptophysin strongly stain the cytoplasm of all the neuroendocrine cells in the pancreatic islets and is also seen in adrenal cortical cells, probably due to a closely related protein.

Useful For: Identification of neuronal tumors and tumors with neuroendocrine differentiation

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Synovial Sarcoma (SS), 18q11.2 (SS18 or SYT) Rearrangement, FISH, Tissue

Clinical Information: Synovial sarcoma (SS) is a malignant soft tissue tumor that predominantly occurs in the lower limbs of children and young adults. This tumor accounts for approximately 5% to 10% of soft tissue tumors, has a poor prognosis, and may occur in other areas of the body such as the head and neck, heart, abdominal wall, mediastinum, and lung, in addition to the extremities. Histologically, SS is grouped either into the monophasic subtype consisting of mostly spindle cells or the biphasic subtype consisting of epithelial and spindle cells. Depending on the site of origin, the differential diagnosis of SS can include mesothelioma, fibrosarcoma, solitary fibrous tumor, leiomyosarcoma, malignant peripheral nerve sheath tumors, epithelioid sarcoma, and clear cell sarcoma. In addition, when the SS is poorly differentiated, the differential diagnosis broadens to include the small round-blue cell tumors (Ewing sarcoma, alveolar rhabdomyosarcoma, and neuroblastoma). Accurate diagnosis of SS is important for appropriate clinical management of patients. Although immunohistochemical markers can be helpful in the correct diagnosis of these various tumor types, recent molecular studies have shown the superior specificity of molecular makers in differentiating SS from other tumors. A recurrent, tumor-specific translocation t(X;18)(p11.2;q11.2) is observed in approximately 90% of synovial sarcomas. A single gene, SS18 (SYT), has been implicated on 18q11.2, while 1 of 3 related genes, SSX1, SSX2, or infrequently SSX4, is usually involved on Xp11.2. The prevalence of SS18-SSX1 is about twice that of SS18-SSX2 in most studies. Detection of these transcripts is usually performed by reverse transcriptase-PCR (RT-PCR) (SYT / Synovial Sarcoma RT-PCR), which allows specific identification of SS18-SSX1 or SS18-SSX2. Identification of the SS18-SSX1 fusion is associated with an unfavorable outcome with significantly shorter overall survival.
when compared to the SS18-SSX2 fusion. Unfortunately, RT-PCR results may be equivocal or falsely negative due to many reasons such as when the available RNA is of poor quality or if a rare translocation partner is present. In these cases, FISH testing can be used to identify SS18 gene rearrangements in these tumors, which supports the diagnosis of SS.

**Useful For:** Supporting the diagnosis of synovial sarcoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the SS18 (SYT) FISH probe. A positive result suggests rearrangement of the SS18 (SYT) gene region at 18q11.2 and supports the diagnosis of synovial sarcoma (SS). A negative result suggests no rearrangement of the SS18 (SYT) gene region at 18q11.2. However, this result does not exclude the diagnosis of SS.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

---

**FSCSC**

---

**Synthetic Cannabinoid Metabolites Screen, Expanded (2019 Scope), Urine**

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-carboxy-AMB-PINACA</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>FUBICA 3,3-dimethylbutanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>5-fluoro-PINAC-ACID</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>4-carboxy-CUMYL-BINACA</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>5-fluoro-PIC-ACID</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>FUBIC-ACID</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>5-fluoro-PINACA 3-methylbutanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
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<td>None Detected</td>
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</tr>
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</tr>
<tr>
<td>FUBINACA 3,3 dimethylbutanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>CHMINACA-3-methylbutanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>4-carboxy-NA-PIM</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>CHMINACA 3,3-dimethylbutanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>CHIMIC-ACID</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
<tr>
<td>5-fluoro-PICA 3,3-dimethylbutanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
</tr>
</tbody>
</table>
Synthetic Glucocorticoid Screen, Random, Urine

Clinical Information: Synthetic glucocorticoids are widely used and have important clinical utility both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these steroids may present with clinical features of Cushing syndrome but with suppressed cortisol levels and evidence of hypothalamus-pituitary-adrenal axis suppression. The fluticasone propionate analyte is reported with this test and is also available separately, see 17BFP / Fluticasone 17-Beta-Carboxylic Acid, Random, Urine for more information.

Useful For: Confirming the presence of the listed synthetic glucocorticoids (see Interpretation)
Confirming the cause of secondary adrenal insufficiency

Interpretation: This test screens for and quantitates, if present, the following synthetic glucocorticoids: betamethasone, budesonide, dexamethasone, fludrocortisone, megestrol acetate, methylprednisolone, prednisolone, prednisone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in urine indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with Cushingoid features.

Reference Values:
Negative
Cutoff concentrations
Betamethasone: 0.10 mcg/dL
Budesonide: 0.20 mcg/dL
Dexamethasone: 0.10 mcg/dL
Fludrocortisone: 0.10 mcg/dL
Fluticasone propionate: 0.10 mcg/dL
Megestrol acetate: 0.10 mcg/dL
Methylprednisolone: 0.10 mcg/dL
Prednisolone: 0.10 mcg/dL
Prednisone: 0.10 mcg/dL
Triamcinolone acetonide: 0.10 mcg/dL

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).

Propionate.

**Useful For:** Confirming the presence of listed synthetic glucocorticoids (see Interpretation) Confirming the cause of secondary adrenal insufficiency

**Interpretation:** This test screens for and quantitates, if present, the following synthetic glucocorticoids: betamethasone, budesonide, dexamethasone, fludrocortisone, megestrol acetate, methylprednisolone, prednisolone, prednisone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in serum indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with Cushingoid features.

**Reference Values:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cutoff concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.20 mcg/dL</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>0.10 mcg/dL</td>
</tr>
</tbody>
</table>

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).

**Clinical References:**

**TPPA 61480 Syphilis Antibody, Treponema pallidum Particle Agglutination, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Syphilis is categorized by an early primary infection in which patients may have nonspecific symptoms and, potentially, genital lesions. Patients tested by serology during the primary phase may be negative for antibodies, especially if testing is performed during the first 1 to 2 weeks after symptom onset. As the disease progresses into the secondary phase, antibodies to T pallidum reach peak titers and may persist indefinitely regardless of the disease state or prior therapy. Therefore, detection of antibodies to non-treponemal antigens, such as cardiolipin (a lipoidal antigen released by host cells damaged by T pallidum) may help to differentiate between active and past syphilis infection. Non-treponemal antibodies are detected by the rapid plasma reagin (RPR) assay, which is typically positive during current infection and negative following treatment.
or during late/latent forms of syphilis. For prenatal syphilis screening, the syphilis IgG test (SYPGN / Syphilis Total Antibody, Serum) is recommended. Testing for IgM-class antibodies to T pallidum should not be performed during routine pregnancy screening unless clinically indicated. Historically, the serologic testing algorithm for syphilis included an initial non-treponemal screening test, such as the RPR or the venereal disease research laboratory (VDRL) tests. Because these tests measure the host's antibody response to non-treponemal antigens, they may lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as fluorescent treponemal antibody absorption (FTA-ABS) or T pallidum particle agglutination (TP-PA). Although the FTA-ABS and TP-PA are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. Due to the low prevalence of syphilis in the United States, the increased specificity of treponemal assays, and the objective interpretation of automated treponemal enzyme immunoassay (EIA) and multiplex flow immunoassay (MFI), many large clinical laboratories have switched to screening for syphilis using a reverse algorithm. Per this algorithm, serum samples are first tested by an automated treponemal assay (eg, EIA or MFI). Specimens testing positive by these assays are then reflexed to the RPR assay to provide an indication of the patient's disease state and history of treatment. Recently, the Centers for Disease Control and Prevention recommended that specimens testing positive by a screening treponemal assay and negative by RPR be tested by a second treponemal test (eg, TP-PA). The results of TP-PA assist in determining whether the results of a screening treponemal test are truly or falsely positive.

**Useful For:** An aid to resolve discrepant results between screening treponemal (eg, enzyme immunoassay [EIA], multiplex flow immunoassay) and non-treponemal (eg, rapid plasma reagin) assays This test is not recommended for general screening purposes for syphilis. This test should not be used to evaluate response to therapy. This test is not intended for medical-legal use.

**Interpretation:** Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for Treponema pallidum specific IgG antibodies using an automated multiplex flow immunoassay (MFI).(1) IgG antibodies to syphilis can remain elevated despite appropriate antimicrobial treatment and a reactive result does not distinguish between recent or past infection. To further evaluate disease and treatment status, samples that are reactive by the syphilis IgG screening test are reflexed to the rapid plasma reagin (RPR) assay, which detects antibodies to cardiolipin, a lipoidal antigen released from host cells damaged by T pallidum.(2) Unlike treponemal-specific antibodies, RPR titers decrease and usually become undetectable following appropriate treatment and can be used to monitor response to therapy. In some patients, the results of the treponemal screening test (syphilis IgG) and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, the Centers for Disease Control and Prevention recommends performing a second treponemal-specific antibody test using a method that is different from the initial screening test (eg, T pallidum particle agglutination; TP-PA).(2) In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios (Table 1). In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG screen (Table 1). If syphilis remains clinically suspected, a second specimen should be submitted, order SYPHT / Syphilis Total Antibody with Reflex, Serum. Table 1. Interpretation and follow-up of reverse screening results Patient history Test and result Interpretation Follow-up EIA/CIA/MFI RPR TP-PA Unknown history of syphilis Non-reactive N/A N/A No serologic evidence of syphilis None, unless clinically indicatedÂ (eg, early syphilis) Unknown history of syphilis Reactive Reactive N/A Untreated or recently treated syphilis See CDC treatment guidelinesÂ Unknown history of syphilis Reactive Non-reactive Non-reactive Probable false-positive screening test Unknown history of syphilis Reactive Non-reactive Non-reactive Probable false-positive screening test No follow-up testing, unless clinically indicated Unknown history of syphilis Reactive Non-reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Known history of syphilis Reactive Non-reactive Reactive or N/A Past, successfully treated syphilis None CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; MFI, multiplex flow immunoassay; N/A, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination.

**Reference Values:**

**Negative**
**Clinical References:**


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**SYPNB** 605983

**Syphilis Total Antibody Bill Only 1 (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

---

**SYPPB** 605984

**Syphilis Total Antibody Bill Only 2 (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

---

**SYPHT** 603259

**Syphilis Total Antibody with Reflex, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial non-treponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's antibody response to non-treponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm as described above, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay, such as an enzyme immunoassay (EIA) and multiplex flow immunoassay (MFI), to detect antibodies specific to T pallidum. If the screening assay is positive, the sample is reflexed to a RPR assay, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for T pallidum specific IgG/IgM antibodies using an automated MFI. A positive treponemal test suggests infection with T pallidum, but does not distinguish between recent or past, or treated and untreated infection. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a non-treponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy. (Table 1) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG/IgM positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, TP-PA). In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios. (Table 1) In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a negative TP-PA result is most consistent with a...
falsely reactive syphilis IgG/IgM screen. If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table 1. Interpretation and follow-up of reverse screening results:

<table>
<thead>
<tr>
<th>Patient history</th>
<th>Syphilis Total Ab by MFI</th>
<th>RPR</th>
<th>TP-PA</th>
<th>Interpretation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown history of syphilis Nonreactive</td>
<td>NA</td>
<td>NA</td>
<td>No serologic evidence of syphilis</td>
<td>None, unless clinically indicated (eg, early/acute/primary syphilis)</td>
<td>Unknown history of syphilis Reactive Reactive Reactive Reactive Nonreactive</td>
</tr>
<tr>
<td>Untreated or recently treated syphilis</td>
<td>See CDC treatment guidelines</td>
<td>None, successfully treated syphilis</td>
<td>None, MFI, multiplex flow immunoassay; NA, not applicable</td>
<td>RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination</td>
<td></td>
</tr>
</tbody>
</table>

**Useful For:** Aiding in the diagnosis of recent or past Treponema pallidum infection Routine prenatal screening This test is not offered as a screening or confirmatory test for blood donor specimens. This test is not useful for diagnosis of congenital syphilis.

**Interpretation:**
- Nonreactive: No serologic evidence of infection to Treponema pallidum (syphilis).
- Repeat testing may be considered in patients with suspected acute or primary syphilis in 2 to 4 weeks.
- Equivocal: Rapid plasma reagin (RPR) has been ordered to help distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result.
- Reactive: RPR has been ordered to help distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result.

**Reference Values:**
- **SYPHILIS TOTAL ANTIBODY**
  - Nonreactive
- **RAPID PLASMA REAGIN SCREEN**
  - Nonreactive
- **RAPID PLASMA REAGIN TITER**
  - Negative
- **SYPHILIS ANTIBODY, Treponema pallidum-PARTICLE AGGLUTINATION**
  - Negative

**Clinical References:**

**Syphilis Total Antibody, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial non-treponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's antibody response to non-treponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed
FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm as described above, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay, such as an enzyme immunoassay (EIA) and multiplex flow immunoassay (MFI), to detect antibodies specific to T pallidum. If the screening assay is positive, the sample is reflexed to a RPR assay, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for T pallidum specific IgG/IgM antibodies using an automated MFI. A positive treponemal test suggests infection with T pallidum but does not distinguish between recent or past, or treated and untreated infection. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a non-treponemal assay, such as RPR, are needed to provide information on a patient’s disease state and history of therapy. (Table 1) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG/IgM positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, TP-PA). In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios. (Table 1) In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG/IgM screen. (Table 1) If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table 1. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis Total Ab by MFI RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of exposure to Treponema pallidum (syphilis). Repeat testing may be considered in patients with suspected acute or primary syphilis. Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Reactive: Results suggest infection with T pallidum at some point in time. Results do not distinguish between recent or past infection, or between treated and untreated syphilis as treponema-specific IgG may remain elevated despite appropriate therapy. Falsely reactive treponemal results may occur; additional testing by a non-treponemal assay is recommended if not previously performed on this sample.

**Reference Values:**

**Nonreactive**


**T, B and NK Lymphocyte Quantitation, New York, Blood**

**Clinical Information:** Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression of CD19, while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3+, CD4+, CD8+), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T-lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia(7) recommend changing the diagnostic criteria for CLL from an absolute lymphocyte count greater than 5 x 10(9)/L to a circulating B-cell count greater than 5 x 10(9)/L(8,9) previously defined in the 1996 National Cancer Institute guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

**Useful For:** Only orderable by New York clients Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution posthematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

**Interpretation:** HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(10,11) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with
CD4 count less than 200 cells/mcL.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**TBET**

**T-Box Expressed in T Cells (TBET) Immunostain, Technical Component Only**

**Clinical Information:** The T-box transcription factor, TBET, is a master regulator of Th1 lymphoid development. It is expressed in other hematopoietic cells including stem cells, B cells, and natural killer cells. In normal tonsil, TBET staining is seen in scattered small interfollicular T lymphocytes, with virtually no staining in the germinal centers. It is preferentially positive in T-cell lymphomas with Th1 differentiation, B-cell lymphomas of memory B-cell origin, and both classical and nodular lymphocyte predominant Hodgkin lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6000 new cases per year or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients with or without concurrent bone marrow involvement. Specific genetic abnormalities are identified in the majority of cases of T-ALL, although many of the classic abnormalities are not detected by conventional chromosome studies and must be identified by fluorescence in situ hybridization (FISH) studies. Each of the genetic subgroups can be critical prognostic markers. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL clone for the prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in T-ALL are listed in the following table.

| Cytogenetic change | Genes involved | Chromosome abnormalities
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>del(1p33)</td>
<td>TAL1/STIL</td>
<td>t(5;14)(q35;q32)</td>
</tr>
<tr>
<td>del(9p)</td>
<td>CDKN2A(p16)</td>
<td>t(11q23;var)</td>
</tr>
<tr>
<td>t(10;11)(p13;q14)</td>
<td>MLLT10(AF10)</td>
<td>PICALM</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.1)</td>
<td>ABL1</td>
<td>Episomal amplification</td>
</tr>
<tr>
<td>t(6;7)(q23;q34)</td>
<td>MYB/TRB</td>
<td>TRB</td>
</tr>
<tr>
<td>t(7;11)(q34;p13)</td>
<td>TRB/LMO2</td>
<td>(t(8;14)(q24.1;q11.2) MYC/TRA D</td>
</tr>
<tr>
<td>t(10;14)(q24;q12)</td>
<td>TLX1(HOX11)/TRAD</td>
<td>t(11;14)(p15;q11.2) LMO1/TRA D</td>
</tr>
<tr>
<td>del(17p)</td>
<td>TP53</td>
<td>Complex karyotype (&gt; or =4 abnormalities)</td>
</tr>
</tbody>
</table>

Useful For: Evaluation of pediatric bone marrow and peripheral blood specimens by fluorescence in situ hybridization probe analysis for classic rearrangements and chromosomal copy number changes associated with T-cell acute lymphoblastic leukemia in patients being considered for enrollment in Children’s Oncology Group clinical trials and research protocols.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 2389
T-Cell Acute Lymphoblastic Leukemia (T-ALL), FISH, Varies

Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients with or without concurrent bone marrow involvement. Specific genetic abnormalities are identified in the majority of cases of T-ALL, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by FISH studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL clone for the prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in T-ALL are listed in the following table.

| Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia Cytogenetic change Genes involved del(1p33) TAL1/STIL t(5;14)(q35;q32) TLX3(HOX11L2)/BCL11B t(10;11)(p13;q14) MLLT10(AF10)/PIICALM Episomal amplification ABL1 del(9p) CDKN2A(p16) t(11q23;var) MLL(KMT2A) t(4;11)(q21;q23) AFF1(AF4)/MLL(KMT2A) t(6;11)(q27;q23) MLLT4(AF6)/MLL(KMT2A) t(9;11)(p22;q23) MLLT3(AF9)/MLL(KMT2A) t(10;11)(p13;q23) MLLT10(AF10)/MLL(KMT2A) t(11;19)(q23;p13.1) MLL(KMT2A)/ELL t(11;19)(q23;p13.3) MLL(KMT2A)/MLLT1(ENL) t(q734;var) TRB t(6;7)(q23;q34) MYB/TRB t(7;10)(q34;q24) TRB/LXL1(HOX11) t(7;11)(q34;p15) TRB/LOM1 t(7;11)(q34;p13) TRB/LOM2 t(14q11.2;var) TRAD t(8;14)(q24.1;q11.2) MYC/TRAD t(10;14)(q24.1;q11.2) TLX1(HOX11)/TRAD t(11;14)(p15;q11.2) LMO1/TRAD t(11;14)(p13;q11.2) LMO2/TRAD del(17p) TP53 Complex karyotype (> or =4 abnormalities)

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with T-cell acute lymphoblastic leukemia (T-ALL), identifying and tracking known chromosome abnormalities in patients with T-ALL and tracking response to therapy. An adjunct to conventional chromosome studies in patients with T-ALL.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.

Clinical References:
1. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Edited by ES Jaffe, NL Harris, H Stein, JW Vardiman. Lyon, IARC Press, 2001
T-Cell Intracellular Antigen 1 (TIA-1) Immunostain, Bone Marrow, Technical Component Only

Clinical Information: T-cell intracellular antigen 1 (TIA-1) shows a granular cytoplasmic staining pattern due to its presence in cytotoxic granules. It is involved in cytotoxic cell-mediated immune responses. TIA-1 was first identified in cytotoxic T cells; it is also expressed in normal natural killer (NK) cells and granulocytes.

Useful For: Characterizing neoplasms of cytotoxic T cells or natural killer cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


T-Cell Intracellular Antigen 1 (TIA-1) Immunostain, Technical Component Only

Clinical Information: T-cell intracellular antigen 1 (TIA-1) shows a granular cytoplasmic staining pattern due to its presence in cytotoxic granules. It is involved in cytotoxic cell-mediated immune responses. TIA-1 was first identified in cytotoxic T cells; it is also expressed in normal natural killer (NK) cells and granulocytes. TIA-1 antibody is useful in characterizing neoplasms of cytotoxic T cells or NK cells.

Useful For: Characterizing neoplasms of cytotoxic T cells or natural killer cells

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

TCL1A

**T-Cell Leukemia/Lymphoma Protein 1A (TCL1A) Immunostain, Technical Component Only**

**Clinical Information:** T-cell leukemia/lymphoma (TCL) proteins augment AKT signal transduction and enhance cell proliferation and survival. Inversion or translocations involving the TCL-1 gene are present in more than 90% of T-cell prolymphocytic leukemias, resulting in overexpression of the TCL-1 protein. TCL-1 is also found in plasmacytoid monocytes in reactive tissues, and the putative malignant counterpart, blastic plasmacytoid dendritic cell neoplasm. In normal tonsil, expression is limited to the B-cell compartment.

**Useful For:** Identification of T-cell leukemia and lymphoma protein overexpression in neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

TLYM

**T-Cell Lymphoma, FISH, Tissue**

**Clinical Information:** T-cell malignancies account for approximately 12% of all non-Hodgkin lymphomas. There are several subtypes of T-cell neoplasms: T-cell acute lymphoblastic leukemia (T-ALL), T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma (PTCL), and various other cutaneous, nodal, and extranodal lymphoma subtypes. The 2 most prevalent lymphoma subtypes are unspecified peripheral T-cell lymphoma (3.7%) and ALCL (2.4%). A few common chromosome abnormalities are associated with specific T-cell lymphoma subtypes, including: Common Chromosome Abnormalities in T-cell Lymphomas Lymphoma Type Chromosome Abnormality FISH Probe Anaplastic Large cell lymphoma (ALCL) 2p23 rearrangement 3α̂/5α̂ ALK 3q28 rearrangement 5α̂/3α̂ TP63 6p25.3 rearrangement 5α̂/3α̂ IRF4 (DUSP22) T-cell prolymphocytic leukemia (TPLL) inv(14)(q11q32)/ t(14;14)(q11;q32) 5α̂/3α̂ TCL1A 5α̂/3α̂ TRAD Hepatosplenic T-cell lymphoma (HSTL) Isochromosome 7q D7S486/D7Z1 trisomy 8 D8Z2/MYC

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various T-cell lymphomas Tracking known chromosome abnormalities and response to therapy in patients with T-cell lymphomas Providing potentially prognostic information in patients with documented systemic anaplastic lymphoma kinase-negative anaplastic large cell lymphoma Supporting the diagnosis of peripheral T-cell lymphoma when coordinated with consultation by anatomic pathology

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone is supportive of a diagnosis of a T-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.
**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Edited by SH Swerdlow, E Campo, NL Harris. IARC, Lyon 2017

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**TLPF 35298**

**T-Cell Lymphoma, FISH, Varies**

**Clinical Information:** T-cell neoplasms are relatively uncommon, accounting for approximately 12% of all non-Hodgkin lymphomas. There are several subtypes of T-cell neoplasms: T-cell acute lymphoblastic leukemia (T-ALL), T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma, and various other cutaneous, nodal, and extranodal lymphoma subtypes. There are a few common chromosome abnormalities associated with specific T-cell lymphoma subtypes evaluated by this FISH test, as follows: Common Chromosome Abnormalities in T-cell Lymphomas Lymphoma Subtype Chromosome Abnormality FISH Probe T-cell prolymphocytic leukemia/lymphoma (T-PLL) inv(14)(q11q32) and t(14;14)(q11;q32) 5'/3'TCL1A Reflex: 14q11.2 rearrangement 5'/3'TRAD Hepatosplenic T-cell lymphoma Isochromosome 7q D7S486/D7Z1 Trisomy 8 D8Z2/MYC These probes have diagnostic relevance and can also be used to track response to therapy.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various T-cell lymphomas Tracking known chromosome abnormalities and response to therapy in patients with T-cell lymphoma

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone supports a diagnosis of a T-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Edited by SH Swerdlow, et al. IARC, Lyon 2017

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**TCRF1 70560**

**T-Cell Receptor Beta (TCR Beta F1) Immunostain, Technical Component Only**

**Clinical Information:** T-cell receptor beta (TCR Beta F1) antibody is directed against the beta chain of the alpha/beta T-cell receptor, thus staining the majority of T lymphocytes. Staining is localized at cell membranes with weak cytoplasmic staining in some cells. Positive staining in malignant lymphomas can confirm T-cell lineage and further subtype as alpha/beta T cells.

**Useful For:** Classification of lymphomas
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TCRGD**

**T-Cell Receptor Delta Immunostain, Technical Component Only**

**Clinical Information:** T-cell receptor delta expression is seen in a small proportion of total T cells. Recognition of T-cell lymphomas that are derived from the delta T-cell subset is important as they often have a more aggressive clinical behavior. Normal tonsils show scattered cells staining in the interfollicular regions.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TREC**

**T-Cell Receptor Excision Circles (TREC) Analysis, Blood**

**Clinical Information:** T cell reconstitution is a critical feature of the recovery of the adaptive immune response and has 2 main components: thymic output of new T cells and peripheral homeostatic expansion of preexisting T cells. It has been shown that though thymic function declines with age, a reasonable output is still maintained into late adult life.(1) In many clinical situations, thymic output is crucial to the maintenance and competence of the T cell effector immune response. Thymic function can be determined by T-cell receptor excision circle (TREC) analysis. TRECs are extrachromosomal DNA byproducts of T-cell receptor (TCR) rearrangement, which are nonreplicative. TRECs are expressed only...
in T cells of thymic origin and each cell is thought to contain a single copy of TREC. Hence, TREC analysis provides a very specific assessment of T-cell recovery (eg, after hematopoietic cell transplantation) or numerical T-cell competence. There are several TRECs generated during the process of TCR rearrangement and the TCR delta deletion TREC (deltaREC psi-J-alpha signal joint TREC) has been shown to be the most accurate TREC for measuring thymic output.(2) This assay measures this specific TREC using quantitative, real-time PCR. Clinical use of TRECs in HIV and Antiretroviral Therapy: HIV infection leads to a decrease in thymic function. Adult patients treated with highly active antiretroviral therapy (HAART) show a rapid and sustained increase in thymic output.(1) Clinical use of TRECs in Hematopoietic Cell Transplantation (HCT) and Primary Immunodeficiencies (PID): Following HCT, there is a period of prolonged immunodeficiency that varies depending on the nature and type of stem cell graft used and the conditioning regimen, among other factors. This secondary immunodeficiency also includes defects in thymopoiesis.(3-5) It has been shown that numerical T cell recovery is usually achieved by day 100 posttransplant, though there is an inversion of the CD4:CD8 ratio that can persist for up to a year.(4) Also, recovery of T-cell function and diversity can take up to 12 months, although this can be more rapid in pediatric patients. However, recovery of T-cell function is only possible when there is numerical reconstitution of T cells. T cells, along with the other components of adaptive immunity, are key players in the successful response to vaccination post-HCT.(6) Recently, it has been shown in patients who received HCT for severe combined immunodeficiency (SCID) that T cell recovery early after stem cell transplant is crucial to long-term T cell reconstitution.(7) Patients who demonstrated impaired reconstitution were shown to have poor early grafting, as opposed to immune failure caused by accelerated loss of thymic output or long-term graft failure. In this study, the numbers of TRECs early after HCT were most predictive for long-term reconstitution. This data suggests that frequent monitoring of T-cell immunity and TREC numbers after HCT can help identify patients who will fail to reconstitute properly, which would allow additional therapies to be instituted in a timely manner.(7) It would be reasonable to extrapolate such a conclusion to other diseases that are also treated by HCT. TREC Copies and Thymic Output in Adults: Since the adult thymus involutes after puberty and is progressively replaced by fat with age, thymus-dependent T cell recovery has been assumed to be severely limited in adults. However, with TREC analysis it has been shown that the change in thymic function in adults is a quantitative phenomenon rather than a qualitative one and thymic output is not totally eliminated.(1,8,9) Thus, after HCT or HAART, the remaining thymic tissue can be mobilized in adults to replenish depleted immune systems with a potentially broader repertoire of naive T cells. Douek et al have shown that there is a significant contribution by the thymus to immune reconstitution after myeloablative chemotherapy and HCT in adults.(8) In fact, this data shows that there is both a marked increase in the TREC numbers and a significant negative correlation of TREC copies with age posttransplant. In addition to the specific clinical situations elucidated above, TREC analysis can be helpful in identifying patients with primary immunodeficiencies and assessing their numerical T-cell immune competence. It can also be used as a measure of immune competence in patients receiving immunotherapy or cancer vaccines, where maintenance of, T-cell output is integral to the immune response against cancer. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(10) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(11-13) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(14) and during summer compared to winter.(15) These data, therefore, indicate that timing and consistency in timing of blood collection are critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Measuring T-cell output or reconstitution (thymopoiesis) following hematopoietic cell transplantation or highly active antiretroviral therapy Evaluating thymic function in patients with cellular or combined primary immunodeficiencies, or receiving immunotherapy or cancer vaccines Assessing T-cell recovery following thymus transplants for DiGeorge syndrome

**Interpretation:** T-cell receptor excision circles (TRECs) generally show an inverse correlation with age, though there can be substantial variations in TREC copies relative to T-cell count within a given age group. Following hematopoietic cell transplantation (HCT), highly active antiretroviral therapy
(HAART), thymic transplants, etc, TREC typically increases from absent or very low levels (below age-matched reference range) to baseline levels or exceeds baseline levels, showing evidence of thymic rebound, which is consistent with recovery of thymic output and T-cell reconstitution. When a patient is being monitored for thymic recovery posttransplant treatment, this assay recommends that a pretransplant (prior to myeloablative or nonmyeloablative conditioning) or a pretreatment baseline specimen be provided so that appropriate comparisons can be made between the pre- and posttransplant treatment specimens. Since there is substantial variability between individuals in TREC copies, the best comparison is made to the patient’s own baseline specimen rather than the reference range (which provides a guideline for TREC copies for age-matched healthy controls). A consultative report will be generated for each patient.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**T-Cell Receptor Gene Rearrangement, PCR, Blood**

**Clinical Information:**
The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.
**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal using blood specimens

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided. Positive, negative, or indeterminate for a clonal T-cell population.

**Clinical References:**

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**TCGBM 31139**

**T-Cell Receptor Gene Rearrangement, PCR, Bone Marrow**

**Clinical Information:** The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearranged to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (e.g., some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions, but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (i.e., polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.

**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided. Positive, negative, or indeterminate for a clonal T-cell population.

**Clinical References:**
**T-Cell Receptor Gene Rearrangement, PCR, Varies**

**Clinical Information:** The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric cell surface TCR, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.

**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal using body fluid or tissue specimens

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population

**Clinical References:**

**T-Cell Subsets, Naive, Memory, and Activated, Blood**

**Clinical Information:** T cells, after completing development and initial differentiation in the thymus, enter the periphery as naive (n) T cells. Naive T cells undergo further differentiation into effector and memory T cells in the peripheral lymphoid organs after recognizing specific antigenic peptides in the context of major histocompatibility (MHC) molecules, through the antigen-specific T-cell receptor. In addition to the cognate signal of the peptide-MHC complex interaction (the term cognate refers to 2 biological molecules that normally interact), T cells require additional costimulatory signals to complete T-cell activation. Naive T cells circulate continuously through the lymph nodes and, on recognition of specific antigen, undergo activation. Due to their antigen-inexperienced state, naive T cells require activation by more potent antigen-presenting cells, such as dendritic cells. Naive T cells can survive in circulation for prolonged periods of time and are very important in contributing to T-cell repertoire diversity. They proliferate in response to interleukin-2, as a consequence of their response to antigen through recognition of peptide-MHC costimulation. These expanded antigen-specific T cells undergo further differentiation into effector cells. The differentiation of naive CD8 T cells into cytotoxic effectors capable of killing target T cells loaded with endogenous peptides on MHC class I molecules may require additional costimulatory signals from CD4 T cells. Naive CD4 T cells also differentiate into different effector subsets such as Th1, Th2, and Th17, which produce specific cytokines.(1) T cells can be subdivided into naive and memory subsets based on the expression of cell-surface markers, such as
CD45RA and CD45RO, among others. It was initially thought that the presence of cell-surface CD45RA indicated the naive subset, while the presence of CD45RO indicated memory subsets. But, it has now been shown that multiple, rather than single, markers are required to distinguish these subsets.(2) Lanzavecchia and Sallusto proposed a model where naive T cells expressing CD45RA and CCR7 lose CD45RA expression on recognition of antigen.(3) The surface markers for identifying naive T-cell subsets include CD45RA, CD62L (L-selectin), and CD27.(4,5) Memory T cells are antigen-experienced cells that are present in greater numbers than antigen-specific precursors, and can respond more efficiently and rapidly to specific antigen. Memory T cells can maintain their populations independent of antigen by homeostatic proliferation in response to cytokines. While there are subcategories of memory T cells based on effector function and cell surface and cytolytic molecule expression, the 2 main categories of memory T cells are central memory T cells (Tcm) and effector memory T cells (Tem).(1,6) Tcm express the CD45RO molecule along with CD62L (L-selectin) and CCR7, and are present mainly in lymphoid tissue.(6,7) They are able to respond to antigen through rapid proliferation and expansion and differentiation into Tem. By themselves, Tcm are not directly effective in effector cytolytic function. Unlike Tcm, Tem express only CD45RO (not CD62L and CCR7).(6) As the name suggests, Tem have remarkable effector function, though they do not proliferate well. Tem are present throughout the circulation in peripheral tissues providing immune surveillance. Memory T cells are particularly important for maintenance of immune competence since they are associated with a rapid and effective response to pathogens. Therefore, depletion of this compartment has more immediate significance than the depletion of naive T cells. Activation of human T cells is critical for the optimal and appropriate performance of T-cell functions within the adaptive immune response. Activated naive T cells undergo proliferation, as well as subsequent differentiation into effector T cells, and are capable of producing cytokines that can modulate the immune response in a variety of ways.(8) There are several markers associated with T-cell activation, but those most commonly used include CD25 (IL-2R)(8) and MHC class II.(9) Additionally, the expression of the costimulatory molecule CD28 augments the T-cell activation response.(10) The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(11) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(12-14) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(15), and during summer compared to winter.(16) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Determining the presence of naive, memory, and activated T cells in various clinical contexts including autoimmune diseases, immunodeficiency states, T-cell recovery post-hematopoietic stem cell transplant, DiGeorge syndrome, and as a measure for T-cell immune competence Naive T-cells results can be used as a surrogate marker for thymic-derived T-cell reconstitution, when used in conjunction with assessment of T-cell receptor excision circles (TREC / T-Cell Receptor Excision Circles [TREC] Analysis, Blood) Assessing a patient's relative risk for infections Evaluation of patients with cellular or combined primary immunodeficiencies Evaluation of T-cell reconstitution after hematopoietic stem cell transplant, chemotherapy, biological therapy, immunosuppression, or immunomodulator therapy Evaluation of patients with autoimmune diseases Evaluation of HIV-positive patients for naive and memory subsets Evaluation of T-cell immune competence (presence of memory and activated T cells) in patients with recurrent infections

Interpretation: Absence or reduction of naive T cells with or without T-cell lymphopenia indicates absent or impaired T-cell reconstitution or thymic output. Reduction in activated T cells can also indicate a reduced T-cell immune competent state. Increases in naive T cells with corresponding decreases in the memory T-cell compartment indicates a failure of further differentiation and effector function or selective loss of memory T cells and an increased risk for infection.

Reference Values: The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Bettelli E, Oukka M, Kuchroo VK: Th17 cells in the circle of immunity

**TREGS**

**T-Cell Subsets, Regulatory (Tregs), Blood**

**Clinical Information:** Regulatory T cells (Tregs) are a population of CD4+ T cells with a unique role in the immune response. Tregs are crucial in suppressing aberrant pathological immune responses in autoimmune diseases, transplantation, and graft-vs-host disease after allogeneic hematopoietic stem cell transplantation. (1) Tregs are activated through the specific T-cell receptor, but their effector function is nonspecific and they regulate the local inflammatory response through cytokine secretion. (2) Tregs secrete interleukin (IL)-9, IL-10, and transforming growth factor-beta 1 (TGF-beta 1), which aid in the mediation of immunosuppressive activity. Chief characteristics of the Treg population are surface expression of the CD25 protein (IL-2Ra) and the intracellular presence of the transcription factor Foxp3. The IL-7 receptor (CD127) is downregulated on Foxp3+CD4+CD25+ T cells and provides an excellent alternative cell-surface marker to Foxp3 for detecting natural Tregs (CD4+CD25+CD127+). (2) Natural Tregs account for 5% to 10% of the total CD4 T-cell population and are derived from thymic precursors. (3) Since CD25 is also expressed on activated T cells, the concomitant use of CD127 permits the differentiation of Tregs from activated T cells. (4) Natural Tregs express the memory marker CD45RO and have limited ability to proliferate. However, within the CD4+CD25+Treg population, there is a subset of Tregs that express the CD45 isoform generally associated with naive T cells (CD45RA), and this subset has been called natural naive (Nn) Tregs. Nn Tregs are most prominent in young adults and decrease with age along with the rest of the naive CD4 T-cell population. (5) Like other naive T cells, Nn Tregs have high proliferative capacity, as well as the suppressor activity of other Treg subsets. Present evidence suggests that Nn Tregs also have a thymic ancestry and are the precursors of the natural Tregs (that are of the memory, antigen-experienced phenotype) and appear to be composed of T cells with self-reactive T-cell receptors. (5) Other subsets of Tregs include the Th3 cells, which secrete high levels of TGF-beta 1 and can be induced by oral administration of antigen, and regulatory T cell 1 (Tr1) cells, which secrete...
interferon-gamma and IL-10. These Treg subsets are most likely induced in the periphery and are responsible for peripheral tolerance to self-antigens. The suppressive activity of Th3 and Tr1 cells are related to the cytokines they produce, TGF-beta 1 and IL-10, respectively. The absence of Tregs as a result of variants in the FOXP3 gene causes a primary immunodeficiency called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance). Patients with IPEX have a complex manifestation of symptoms including severe watery diarrhea due to significant villous atrophy and lymphocytic infiltration of bowel mucosa, early-onset autoimmune endocrinopathies involving the pancreas or thyroid, and a dermatitic (eczematous) rash. In addition, there are other autoimmune manifestations including autoimmune cytopenias and autoimmune hepatitis. Renal disease is quite common in these patients. Finally, these patients also have a significant predisposition to infections including sepsis, pneumonia, meningitis, and osteomyelitis. Decreased Foxp3+CD4+CD25+Tregs have been reported in 1 patient with a STAT5b alteration. There is an expansion of Nn Tregs in patients with monoclonal gammopathy of undetermined significance and multiple myeloma, likely as a response to the process of malignant transformation. Expansion of Tregs has also been reported in other neoplasias including B-cell chronic lymphocytic leukemia, Hodgkin disease, and solid tumors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to negatively correlate with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Evaluating patients with clinical features of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance) and other primary immunodeficiencies, autoimmune diseases, allergy and asthma, and graft-vs-host disease post-hematopoietic stem cell transplantation

**Interpretation:** The lack of regulatory TÂ cells (Tregs) is associated with variants in the FOXP3 gene. Low Tregs are also seen in the context of STAT5b alterations. Reduced Nn Tregs and natural Tregs are likely to predispose to autoimmunity, while reductions in Th3/Tr1 cells may impair oral and peripheral tolerance, also facilitating the development of autoimmunity. The presence of expanded naive Tregs may indicate a process of malignant transformation, if other clinical features of malignant disease are present. Increased Tregs in donor stem cell allografts have been associated with a reduced incidence of graft-versus-host disease (ie, mediating a protective effect) after allogeneic stem cell transplantation.

**Reference Values:** The appropriate age-related reference values will be provided on the report.

**Clinical References:**
T-Lymphoblastic Leukemia/Lymphoma, FISH, Tissue

Clinical Information: T-lymphoblastic lymphoma (T-LBL) is the non-leukemic form of T-acute lymphoblastic leukemia (T-ALL). In the United States, the incidence of ALL is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70 percent of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric ALL cases are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma, approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL characteristically presents in adolescents and young adults as a mediastinal mass with or without concurrent bone marrow involvement. It is not uncommon that the only sample available with T-LBL involvement is a paraffin-embedded mediastinal or lymph node biopsy specimen. Specific genetic abnormalities can be identified in the majority of T-ALL/LBL cases, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by fluorescence in situ hybridization (FISH) studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL/LBL clone for prognostic genetic subgroups.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with T-cell lymphoblastic leukemia or lymphoma

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result is not diagnostic for T-lymphoblastic lymphoma (T-LBL), but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.


TPIT Immunostain, Technical Component Only

Clinical Information: T-PIT is the transcription factor of functioning and silent corticotroph
adenomas and is useful for the diagnosis of corticotroph adenoma and null cell adenoma. T-PIT may be included as part of a panel along with transcription factors SF-1 and Pit-1 to identify null cell adenomas (all negative).

**Useful For:** Diagnosis of corticotroph, silent corticotroph, and null cell adenomas of the pituitary

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


### T3 (Triiodothyronine), Free, Serum

**Clinical Information:** Normally triiodothyronine (T3) circulates tightly bound to thyroxine-binding globulin and albumin. Only 0.3% of the total T3 is unbound (free); the free fraction is the active form. In hyperthyroidism, both thyroxine (tetraiodothyronine; thyroxine: T4) and T3 levels (total and free) are usually elevated, but in a small subset of hyperthyroid patients (T3 toxicosis) only T3 is elevated. Generally, free T3 (FT3) measurement is not necessary since total T3 will suffice. However, FT3 levels may be required to evaluate clinically euthyroid patients who have an altered distribution of binding proteins (eg, pregnancy, dysalbuminemia). Some investigators recommend the FT3 assay for monitoring thyroid replacement therapy, although its clinical role is not precisely defined.

**Useful For:** Free triiodothyronine (T3) is a second- or third-level test of thyroid function; it provides further confirmation of hyperthyroidism, supplementing the tetraiodothyronine (T4), sensitive thyrotropin (sTSH), and total T3 assays. Evaluating clinically euthyroid patients who have an altered distribution of binding proteins. Monitoring thyroid hormone replacement therapy

**Interpretation:** Elevated free triiodothyronine (FT3) values are associated with thyrotoxicosis or excess thyroid hormone replacement.

**Reference Values:**

> or =1 year: 2.8-4.4 pg/mL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html


### T3 (Triiodothyronine), Reverse, Serum

**Clinical Information:** Reverse triiodothyronine (rT3) differs from triiodothyronine (T3) in the positions of the iodine atoms attached to the aromatic rings. The majority of rT3 found in the circulation is formed by peripheral deiodination (removal of an iodine atom) of T4 (thyroxine). rT3 is believed to...
be metabolically inactive. The rT3 level tends to follow the T4 level: low in hypothyroidism and high in hyperthyroidism. Additionally, increased levels of rT3 have been observed in starvation, anorexia nervosa, severe trauma and hemorrhagic shock, hepatic dysfunction, postoperative states, severe infection, and in burn patients (i.e., sick euthyroid syndrome). This appears to be the result of a switchover in deiodination functions with the conversion of T4 to rT3 being favored over the production of T3.

**Useful For:** Aiding in the diagnosis of the sick euthyroid syndrome

**Interpretation:** In hospitalized or sick patients with low triiodothyronine (T3) values, elevated reverse triiodothyronine (rT3) values are consistent with sick euthyroid syndrome. Also, the finding on an elevated rT3 level in a critically ill patient helps exclude a diagnosis of hypothyroidism. The rT3 is high in patients on medications such as propylthiouracil, ipodate, propranolol, amiodarone, dexamethasone, and the anesthetic agent halothane. Dilantin decreases rT3 due to the displacement from thyroxine-binding globulin, which causes increased rT3 clearance. To convert from ng/dL to nmol/L, multiply the ng/dL result by 0.01536.

**Reference Values:**
10-24 ng/dL

**Clinical References:**

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**T3 (Triiodothyronine), Total, Serum**

**Clinical Information:** Thyroid hormones regulate a number of developmental, metabolic, and neural activities throughout the body. The thyroid gland synthesizes 2 hormones. The 2 main hormones secreted by the thyroid gland are thyroxine, which contains 4 atoms of iodine (T4), and triiodothyronine (T3). T3 production in the thyroid gland constitutes approximately 20% of the total T3; the rest is generated by the conversion (deiodination) of T4 to T3 is also produced by conversion (deiodination) of T4 in peripheral tissues. Circulating levels of T4 are much greater than T3 levels, but T3 is biologically the most metabolically active hormone (3-4 times more potent than T4) although its effect is briefer due to its shorter half-life compared to T4. Thyroid hormones circulate primarily bound to carrier proteins (e.g., thyroid-binding globulin: TBG, prealbumin, and albumin); whereas only a small fraction circulates unbound (free). Only the free forms are metabolically active. While both T3 and T4 are bound to TBG, T3 is bound less firmly than T4. Total T3 consists of both the bound and unbound fractions. In hyperthyroidism, both T4 and T3 levels are usually elevated, but in a small subset of hyperthyroid patients, only T3 is elevated (T3 toxicosis). In hypothyroidism T4 and T3 levels are decreased. T3 levels are frequently low in sick or hospitalized euthyroid patients. See Thyroid Function Ordering Algorithm in Special Instructions.

**Useful For:** Second-order testing for hyperthyroidism in patients with low thyroid-stimulating hormone values and normal thyroxine levels Diagnosis of triiodothyronine toxicosis This test is not useful for general screening of the population without a clinical suspicion of hyperthyroidism.

**Interpretation:** Triiodothyronine (T3) values above 200 ng/dL in adults or over age related cutoffs in children are consistent with hyperthyroidism or increased thyroid hormone-binding proteins. Abnormal levels (high or low) of thyroid hormone-binding proteins (primarily albumin and thyroid-binding globulin) may cause abnormal T3 concentrations in euthyroid patients.

**Reference Values:**

**Pediatric**

- 0-5 days: 73-288 ng/dL
- 6 days-2 months: 80-275 ng/dL
- 3-11 months: 86-265 ng/dL
- 1-5 years: 92-248 ng/dL
- 6-10 years: 93-231 ng/dL
11-19 years: 91-218 ng/dL

Adult (> or =20 years): 80-200 ng/dL

For SI unit Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html


**T4 (Thyroxine), Free, Dialysis, Serum**

Clinical Information: Thyroxine (T4) and triiodothyronine (T3) are the 2 biologically active thyroid hormones. T4 makes up more than 80% of circulating thyroid hormones. Following secretion by the thyroid gland, approximately 70% of circulating T4 and T3 are bound to thyroid-binding globulin (TBG), while 10% to 20% each are bound to transthyretin (TTR) and albumin, respectively. Less than 0.1% circulates as free T4 (FT4) or free T3 (FT3). FT4 and FT3 enter and leave cells freely by diffusion. Only the free hormones are biologically active, but bound and free fractions are in equilibrium. Equilibrium with TTR and albumin is rapid. By contrast, TBG binds thyroid hormones very tightly and equilibrium dissociation is slow. Biologically, TBG-bound thyroid hormone serves as a hormone reservoir and T4 serves as a prohormone for T3. Within cells, T4 is either converted to T3, which is about 5 times as potent as T4, or reverse T3, which is biologically inactive. Ultimately, T3, and to a much lesser degree T4, bind to the nuclear thyroid hormone receptor, altering gene expression patterns in a tissue-specific fashion. Under normal physiologic conditions, FT4 and FT3 exert direct and indirect negative feedback on pituitary thyrotropin (thyroid-stimulating hormone: TSH) levels, the major hormone regulating thyroid gland activity. This results in tight regulation of thyroid hormone production and constant levels of FT4 and FT3 independent of the binding protein concentration. Measurement of FT4 and FT3, in conjunction with TSH measurement, therefore represents the best method to determine thyroid function status. It also allows determination of whether hyperthyroidism (increased FT4) or hypothyroidism (low FT4) are primary (the majority of cases, TSH altered in the opposite direction as FT4) or secondary/tertiary (hypothalamic/pituitary origin, TSH altered in the same direction as FT4). By contrast, total T4 and T3 levels can vary widely as a response to changes in binding protein levels, without any change in free thyroid hormone levels and, hence, actual thyroid function status. FT4 is usually measured by automated analog immunoassays. In most instances, this will result in accurate results. However, abnormal types or quantities of binding proteins found in some patients and most often related to other illnesses or drug treatments, may interfere in the accurate measurement of FT4 by analog immunoassays. These problems can be overcome by measuring FT4 by equilibrium dialysis, free from interfering proteins.

Useful For: Determining thyroid status of sick, hospitalized patients

Interpretation: All free hormone assays should be combined with thyrotropin (thyroid-stimulating hormone) measurements. Free thyroxine (FT4) levels below 0.8 ng/dL indicate possible hypothyroidism. FT4 levels above 2.0 ng/dL indicates possible hyperthyroidism. Neonates can have significantly higher FT4 levels. The hypothalamic-pituitary-thyroid axis can take several days or, sometimes, weeks to mature.

Reference Values: 0.8-2.0 ng/dL

Reference values apply to all ages.


**FRT4**

**T4 (Thyroxine), Free, Serum**

**Clinical Information:** Free thyroxine (FT4) comprises a small fraction of total thyroxine. FT4 is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

**Useful For:** Evaluation of suspected thyroid function disorders using free thyroxine measured together with thyroid-stimulating hormone

**Interpretation:** Elevated values suggest hyperthyroidism or exogenous thyroxine. Decreased values suggest hypothyroidism. Free thyroxine (FT4) works well to correct total T4 values for thyroxine-binding globulin alterations, but may give misleading values when abnormal binding proteins are present or the patient has other major illnesses (euthyroid sick syndrome).

**Reference Values:**

Pediatric
- 0-5 days: 0.9-2.5 ng/dL
- 6 days-2 months: 0.9-2.2 ng/dL
- 3-11 months: 0.9-2.0 ng/dL
- 1-5 years: 1.0-1.8 ng/dL
- 6-10 years: 1.0-1.7 ng/dL
- 11-19 years: 1.0-1.6 ng/dL

Adult (> or =20 years): 0.9-1.7 ng/dL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html


**T4FT4**

**T4 (Thyroxine), Total and Free, Serum**

**Clinical Information:** THYROXINE (T4), TOTAL: T4 is synthesized in the thyroid gland. T4 is metabolized to T3 peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free or unbound portion. The remainder is bound to thyroxine-binding globulin (TBG), prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted peripherally to triiodothyronine (T3). High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism), and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein binding abnormalities. However, changes in binding proteins can occur which affect the level of total T4 but leave the level of unbound hormone unchanged. THYROXINE (T4), FREE: Free thyroxine comprises a small fraction of total thyroxine. The free T4 (FT4) is available to the tissues and is, therefore, the metabolically active

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fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

**Useful For:** Thyroxine (T4) and free T4 are measured together with thyroid-stimulating hormone when thyroid function disorders are suspected.

**Reference Values:**

T4 (THYROXINE), TOTAL ONLY
- Adult (> or =20 years): 4.5-11.7 mcg/dL
- Pediatric:
  - 0-5 days: 5.0-18.5 mcg/dL
  - 6 days-2 months: 5.4-17.0 mcg/dL
  - 3-11 months: 5.7-16.0 mcg/dL
  - 1-5 years: 6.0-14.7 mcg/dL
  - 6-10 years: 6.0-13.8 mcg/dL
  - 11-19 years: 5.9-13.2 mcg/dL

T4 (THYROXINE), FREE
- Adult (> or =20 years of age): 0.9-1.7 ng/dL
- Pediatric:
  - 0-5 days: 0.9-2.5 ng/dL
  - 6 days-2 months: 0.9-2.2 ng/dL
  - 3-11 months: 0.9-2.0 ng/dL
  - 1-5 years: 1.0-1.8 ng/dL
  - 6-10 years: 1.0-1.7 ng/dL
  - 11-19 years: 1.0-1.6 ng/dL

necessary to determine if thyrotropin, TBG, or free T4 testing is needed.

**Reference Values:**

**Pediatric**
- 0-5 days: 5.0-18.5 mcg/dL
- 6 days-2 months: 5.4-17.0 mcg/dL
- 3-11 months: 5.7-16.0 mcg/dL
- 1-5 years: 6.0-14.7 mcg/dL
- 6-10 years: 6.0-13.8 mcg/dL
- 11-19 years: 5.9-13.2 mcg/dL
- Adult (> or =20 years): 4.5-11.7 mcg/dL

For SI unit Reference Values, see [www.mayocliniclabs.com/order-tests/si-unit-conversion.html](http://www.mayocliniclabs.com/order-tests/si-unit-conversion.html)

**Clinical References:**

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**Tacrolimus, Blood**

**Clinical Information:** Tacrolimus is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by CYP3A4, thus its concentrations are affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range, and adverse effects are common, particularly at high dose and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in stable patients for most solid organ transplants. Trough concentrations should be maintained below 20 ng/mL.

**Useful For:** Monitoring whole blood tacrolimus concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to tacrolimus with trough whole blood levels of 5.0 to 15.0 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. Therapeutic ranges are based on samples drawn at trough (ie, immediately before a scheduled dose). Blood drawn at other times will yield higher results. The assay is specific for tacrolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, sirolimus, sirolimus metabolites, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**
- 5.0-15.0 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

**Clinical References:**
2. Scott LJ, McKeage
Tacrolimus, Peak, Blood

Clinical Information: Tacrolimus (Prograf) is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by CYP3A4; thus, its concentration is affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range and adverse effects are common, particularly at high dose and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in solid organ transplant patients who are stable. Trough concentrations should be maintained below 20 ng/mL. Optimal postdose sampling strategies and blood concentrations have not been well established for tacrolimus. A study of 54 liver transplant patients suggested that most individuals have tacrolimus blood concentrations ranging between 5.0 and 30.0 ng/mL in samples drawn 1 to 4 hours after dosing, although some patients showed slightly higher blood concentrations at 1-hour postdose.

Useful For: Assessment of postdosing (peak) blood tacrolimus concentrations

Interpretation: This test measures postdose levels of tacrolimus. Established reference ranges reflect trough measurement, and are not applicable to samples drawn after dosing. No reference ranges or standard sampling protocols have been established for postdosing tacrolimus levels, but a limited study of liver transplant recipients suggests most patients will show postdose tacrolimus levels ranging from 5.0 to 30.0 ng/mL when drawn 1 to 4 hours after dosing. The narrow therapeutic window and high individual pharmacokinetic variability of tacrolimus make regulation of dose by blood concentrations essential. Since 90% of the drug is in the cellular components of blood, especially erythrocytes, whole blood, rather than plasma, concentrations are measured and correlate better with efficacy and toxicity. This assay is specific for tacrolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, sirolimus, sirolimus metabolites, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry (LC-MS/MS) are approximately 30% less than by immunoassay.

Reference Values: 5.0-30.0 ng/mL

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs or symptoms of rejection or toxicity.


Tapentadol and Metabolite, Random, Urine

Clinical Information: Tapentadol, a centrally acting opioid analgesic, is used in the treatment of moderate to severe acute and chronic pain and for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults (extended release formulation only). Tapentadol acts as an opiate agonist through its binding to mu-opioid receptors and through the inhibition of norepinephrine
reuptake. About 97% of the parent drug is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. Tapentadol and its metabolites (N-desmethyltapentadol and hydroxyl-tapentadol) are excreted almost exclusively via the kidneys and approximately 70% of the drug is excreted in urine in the conjugated form. The metabolites of tapentadol have no analgesic activity. The half-life of tapentadol is approximately 4 hours. Opioid analogesics have high abuse potential and the regular use of tapentadol may result in physical dependence and tolerance. Tapentadol is a schedule II controlled substance with abuse liability similar to other opioid agonists.

**Useful For:** Monitoring of compliance utilizing tapentadol Detection and confirmation of the illicit use of tapentadol

**Interpretation:** The presence of tapentadol or N-desmethyltapentadol levels of 25 ng/mL or higher is a strong indicator that the patient has used tapentadol.

**Reference Values:**
Cutoff: 25 ng/mL

Note: Tapentadol concentrations will be reported quantitatively and N-desmethyltapentadol will be reported qualitatively (Present or Negative).

**Clinical References:**

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**Tapioca IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 Åêâ–¬åêœ 0.69 Low Positive 2 0.70 Åêâ–¬åêœ 3.49 Moderate Positive 3 3.50 Åêâ–¬åêœ 17.49 Positive 4 17.50 Åêâ–¬åêœ 49.99 Strong Positive 5 50.00 Åêâ–¬åêœ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Targeted Benzodiazepine Screen, Random, Urine**

**Clinical Information:** Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures, and they are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent and metabolites in the urine.

**Useful For:** Determining compliance or identifying illicit benzodiazepine drug use This test is not intended for employment-related testing.

**Interpretation:** If a benzodiazepine or its corresponding metabolites is identified (present), it indicates that the patient has used the respective benzodiazepine in the recent past. The absence of expected benzodiazepines or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional
Reference Values:
Not Detected

Cutoff concentrations:
- Alprazolam: 10 ng/mL
- Alpha-Hydroxyalprazolam: 10 ng/mL
- Alpha-Hydroxyalprazolam Glucuronide: 50 ng/mL
- Chlordiazepoxide: 10 ng/mL
- Clobazam: 10 ng/mL
- N-Desmethylclobazam: 200 ng/mL
- Clonazepam: 10 ng/mL
- 7-Aminoclonazepam: 10 ng/mL
- Diazepam: 10 ng/mL
- Nordiazepam: 10 ng/mL
- Flunitrazepam: 10 ng/mL
- 7-Aminoflunitrazepam: 10 ng/mL
- Flurazepam: 10 ng/mL
- 2-Hydroxy Ethyl Flurazepam: 10 ng/mL
- Lorazepam: 10 ng/mL
- Lorazepam Glucuronide: 50 ng/mL
- Midazolam: 10 ng/mL
- Alpha-Hydroxy Midazolam: 10 ng/mL
- Oxazepam: 10 ng/mL
- Oxazepam Glucuronide: 50 ng/mL
- Prazepam: 10 ng/mL
- Temazepam: 10 ng/mL
- Temazepam Glucuronide: 50 ng/mL
- Triazolam: 10 ng/mL
- Alpha-Hydroxy Triazolam: 10 ng/mL
- Zolpidem: 10 ng/mL
- Zolpidem Phenyl-4-Carboxylic acid: 10 ng/mL

Clinical References:

Targeted Benzodiazepine Screen, Urine

Clinical Information: Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures, and they are also used in pain management. With a high risk for abuse/diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent and metabolites in the urine.

Useful For: Qualitatively (present vs. not detected) identifying 27 benzodiazepine compounds (parent drug and metabolites) in urine to help determine compliance or identify illicit benzodiazepine drug use Not intended for use in employment-related testing

Interpretation: If a benzodiazepine or its corresponding metabolites is identified (present), it
indicates that the patient has used the respective benzodiazepine in the recent past. The absence of expected benzodiazepines or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

Reference Values:
Only orderable as part of profile. For more information see:
CSMPU / Controlled Substance Monitoring Panel, Random, Urine
TBSU / Targeted Benzodiazepine Screen, Random, Urine

Not Detected

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-Hydroxyalprazolam: 10 ng/mL
Alpha-Hydroxyalprazolam Glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL
N-Desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy Ethyl Flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam Glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-Hydroxy Midazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam Glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam Glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-Hydroxy Triazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem Phenyl-4-Carboxylic acid: 10 ng/mL


TOPSU 65059

Targeted Opioid Screen, Random, Urine

Clinical Information: Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are
found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression depending on the dose. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay doesn't hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone).

**Useful For:** Qualitatively (present vs. not detected) identifying 33 opioid compounds (parent drug and metabolites) in urine to help determine compliance or identify illicit opioid drug use. This test is not intended for use in employment-related testing.

**Interpretation:** If an opioid or its corresponding metabolites is identified (present), it indicates that the patient has used the respective opioid in the recent past. The absence of expected opioids or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

**Reference Values:**

Only orderable as part of profile. For more information see:
- CSMPU / Controlled Substance Monitoring Panel, Random, Urine
- TOSU / Targeted Opioid Screen, Random, Urine

Not Detected

Cutoff concentrations:
- Codeine: 25 ng/mL
- Codeine-6-beta-glucuronide: 100 ng/mL
- Morphine: 25 ng/mL
- Morphine-6-beta-glucuronide: 100 ng/mL
- 6-Monoacetylmorphine: 25 ng/mL
- Hydrocodone: 25 ng/mL
- Norhydrocodone: 25 ng/mL
- Dihydrocodeine: 25 ng/mL
- Hydromorphone: 25 ng/mL
- Hydromorphone-3-beta-glucuronide: 100 ng/mL
- Oxycodone: 25 ng/mL
- Noroxycodone: 25 ng/mL
- Oxymorphone: 25 ng/mL
- Oxymorphone-3-beta-glucuronide: 100 ng/mL
- Noroxymorphone: 25 ng/mL
- Fentanyl: 2 ng/mL
- Norfentanyl: 2 ng/mL
- Meperidine: 25 ng/mL
- Normeperidine: 25 ng/mL
- Naloxone: 25 ng/mL
- Naloxone-3-beta-glucuronide: 100 ng/mL
- Methadone: 25 ng/mL
- EDDP: 25 ng/mL
- Propoxyphene: 25 ng/mL
- Norpropoxyphene: 25 ng/mL
- Tramadol: 25 ng/mL
- O-desmethyltramadol: 25 ng/mL
- Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL


Targeted Opioid Screen, Random, Urine

Clinical Information: Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression depending on the dose. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intramuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay doesn't hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone).

Useful For: Determining compliance or identifying illicit opioid drug use using urine specimens This test is not intended for employment-related testing.

Interpretation: If an opioid or its corresponding metabolites is identified (present), it indicates that the patient has used the respective opioid in the recent past. The absence of expected opioids or their metabolites indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.


Targeted Stimulant Screen, Random, Urine

Clinical Information: Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All of the other amphetamines (eg, methylenedioxyamphetamine: MDMA) are Drug Enforcement Administration (DEA) scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or
methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

**Useful For:** Aiding in the determination of compliance or identify illicit stimulant drug use This test is not intended for use in employment-related testing.

**Interpretation:** If a stimulant or its corresponding metabolite is identified (present), it indicates that the patient has used the respective stimulant in the recent past (typically 1-3 days). The absence of the expected stimulant or its metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within two weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

**Reference Values:**
Only orderable as part of profile. For more information see:
- CSMPU / Controlled Substance Monitoring Panel, Random, Urine
- TSPU / Targeted Stimulant Screen, Random, Urine

Not Detected

Cutoff concentrations:
- Methamphetamine: 100 ng/mL
- Amphetamine: 100 ng/mL
- 3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
- 3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
- 3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
- Ephedrine: 100 ng/mL
- Pseudoephedrine: 100 ng/mL
- Phentermine: 100 ng/mL
- Phencyclidine (PCP): 20 ng/mL
- Methylphenidate: 20 ng/mL
- Ritalinic acid: 100 ng/mL

**Clinical References:**
**Targeted Stimulant Screen, Random, Urine**

**Clinical Information:** Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All of the other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug and Enforcement Administration (DEA) scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

**Useful For:** Determining compliance or identifying illicit stimulant drug use. This test is not intended for employment-related testing.

**Interpretation:** If a stimulant or its corresponding metabolite is identified (present), it indicates that the patient has used the respective stimulant in the recent past (typically 1-3 days). The absence of the expected stimulant or its metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within two weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

**Reference Values:**

Not detected

Cutoff concentrations

- Methamphetamine: 100 ng/mL
- Amphetamines: 100 ng/mL
- 3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
- 3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
- 3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
- Ephedrine: 100 ng/mL
- Pseudoephedrine: 100 ng/mL
- Phentermine: 100 ng/mL
- Phencyclidine (PCP): 20 ng/mL
- Methylphenidate: 20 ng/mL
- Ritalinic acid: 100 ng/mL

**Clinical References:**

8. Chronic Pain in America: Roadblocks to Relief, survey conducted for the American Pain Society, The American Academy
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to taragon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

distinguishing hairy cell leukemia from other types of B-cell lymphomas. Caution should be used since other types of lymphoma can also be positive, such as marginal zone lymphoma, but usually their staining is less intense. Normal mast cells also express TRAP.

**Useful For:** Classification of leukemias and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TAU3**

**TAU 3 Immunostain, Technical Component Only**

**Clinical Information:** The Tau 3 antibody stains microtubule-associated proteins in the brain that are associated with diseases of the central nervous system, especially neurodegenerative disorders.

**Useful For:** Diagnosis of neurodegenerative disorders

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

---

**TAU4**

**TAU 4 Immunostain, Technical Component Only**

**Clinical Information:** The Tau 4 antibody stains microtubule-associated proteins in the brain that are associated with diseases of the central nervous system, especially neurodegenerative disorders.

**Useful For:** Diagnosis of neurodegenerative disorders
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**TAU Immunostain, Technical Component Only**

**Clinical Information:** Tau proteins are microtubule-associated proteins that regulate the dynamics of the microtubule network, and are especially involved in the axonal transport and neuronal plasticity. Antibodies to Tau proteins stain the tangles of microtubules associated with Alzheimer cytoskeletal pathology; neurofibrillary tangles, neuropil threads, and neuritic ("senile") plaques (NPs). Tau has become important in the analysis of a wide variety of neurodegenerative disorders, including Alzheimer disease, Pick disease, corticobasal degeneration, supranuclear palsy, multisystem atrophy, as well as a recently recognized category of disorders known as tauopathies.

**Useful For:** Analysis of neurodegenerative disorders

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Tay-Sachs Disease, HEXA Gene, Full Gene Analysis, Varies**

**Clinical Information:** Tay-Sachs disease (TSD) is an inherited lysosomal storage disease caused by a deficiency of the enzyme beta-hexosaminidase A. It is characterized by accumulation of GM2 gangliosides in the brain and central nervous system. The HEXA gene encodes the alpha subunit of beta-hexosaminidase A and mutations in this gene cause TSD. TSD occurs in approximately 1 in 200,000 live births with a carrier frequency of 1 in 250 to 1 in 300 in the general population. The carrier frequency for this disease in individuals of Ashkenazi Jewish ancestry is 1 in 31. The classic form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations include progressive...
neurodegeneration, seizures, and blindness, leading to total incapacitation and death. The subacute and adult-onset types of TSD are characterized by later ages of onset and a broad spectrum of disease symptoms and severity. TSD is inherited in an autosomal recessive manner. Several common mutations in the HEXA gene account for 92% of disease-causing mutations in the Ashkenazi Jewish population. Testing for these mutations is available as a panel, TSDP / Tay-Sachs Disease, Mutation Analysis, HEXA. In non-Ashkenazi Jewish individuals, the detection rate for the common mutations is significantly decreased. Sequencing of the entire HEXA gene detects less common disease-causing mutations. The recommended first-tier test for TSD carrier screening and diagnosis in all patients is a biochemical test that measures hexosaminidase A activity in white blood cells, NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes.

**Useful For:** Second-tier test for confirming a biochemical diagnosis of Tay-Sachs disease (TSD)
Carrier testing of individuals with a family history of TSD but an affected individual is not available for testing or disease-causing mutations have not been identified Testing individuals with enzyme activity consistent with carrier status but negative molecular testing by a panel of common mutations

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Gene, Full Gene Analysis.

**Useful For:** Carrier testing of individuals of Ashkenazi Jewish ancestry or who have a family history of Tay-Sachs disease Determining Tay-Sachs disease carrier status for individuals with enzyme activity within the carrier or equivocal ranges Prenatal diagnosis of Tay-Sachs disease for at-risk families Confirmation of suspected clinical diagnosis of Tay-Sachs disease in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

TCRVB 62930

**TCR V-Beta Repertoire Analysis by Spectratyping, Blood**

**Clinical Information:** The rearrangement of the T-cell receptor (TCR) through somatic recombination of V (variable), D (diversity), J (joining), and C (constant) regions is a defining event in the development and maturation of a T cell. TCR gene rearrangement takes place in the thymus. During the process of rearrangement, DNA byproducts are generated called T-cell receptor excision circles (TRECs) and these are used as markers of T cells that have recently emigrated from the thymus (TREC / T-Cell Receptor Excision Circles [TREC] Analysis, Blood). T cells, as part of the adaptive immune system, recognize foreign antigens when they are displayed on the surface of the body's own cells. T cells recognize these foreign antigens as peptides presented in the context of major histocompatibility complex (MHC) molecules through their T-cell receptors. Each TCR exists as 2 different polypeptide chains (heterodimers) called the TCR alpha chain and TCR beta chain, and these are linked by disulfide bonds. The majority of T cells (approximately 90%) in the body express TCRs with alpha and beta chains. A minority of T cells express other T-cell receptors made of different polypeptide chains, gamma and delta. Each T cell has approximately 30,000 identical antigen receptors on its cell surface. A TCR has only 1 antigen-binding site, in contrast to the B-cell receptor, which has 2, and TCRs are never secreted and always remain on the cell surface. The alpha and beta chains are encoded by different gene loci (alpha and beta TCR gene locus). The beta chain locus rearranges before the alpha chain and a functional beta chain has to be produced in order for the T cell to form a pre-T-cell receptor. The expression of the rearranged beta chain with an alpha chain precursor suppresses additional gene rearrangement at the TCR beta locus. The TCR alpha chain locus rearrangement can proceed even with production of a functional alpha chain until there is positive selection of the particular T cell. However, it is important to note that each T cell has a single functional specificity for its TCR. A key concept in understanding the immune response is that there is enormous diversity in the immune system to enable protection against a huge array of pathogens. Since the germline genome is limited in size, diversity is achieved not only by the process of V(D)J recombination but also by junctional (junctions between V-D and D-J segments) deletion of nucleotides and addition of pseudo-random, nontemplated nucleotides. In particular, the CDR3 (complementarity determining region 3), which is the most critical determinant of antigenic specificity in T cells (and also B cells) is short (between 66-90 nucleotides, approximately 20-30 amino acids) and amenable to assessment of length by fragment length analysis, which provides a size resolution of up to 1 base pair between different CDR3 regions. It is thought that the CDR3-TCR beta chain repertoire in healthy adults contains somewhere between 3 and 4 million unique sequences.(1) Other reports suggest that the unique TCR repertoire after thymic selection is between 10 to 100 million in humans.(2) There is, however, a bias in TCR selection with overrepresentation of certain TCRs that are widely used in individuals who share the same major histocompatibility (MHC) types and these are called "public TCRs." Public TCRs generally have fewer random nucleotide additions in their sequence. The TCR V beta repertoire varies significantly between individuals and populations because of 7 frequently occurring inactivating polymorphisms in functional gene segments and a large insertion/deletion-related polymorphism encompassing 2 V beta gene segments. With this
latter situation, the TCR Vb 6-2/6-3 and TCR Vb 4-3 genes are frequently deleted from all ethnic groups. It has been reported that the total number of functional TCR V beta gene segments expressed by an individual varies from 42 to 47. Deep sequencing technologies are evolving to analyze this large diversity in the adaptive immune receptors; however, deep sequencing of the T-cell and B-cell receptor genes is not yet widely available and is expensive. Flow cytometry-based analysis to assess TCR V beta diversity is available; however, the antibodies are limited and therefore the assay is not capable of assessing the entire TCR V beta repertoire. On the other hand, TCR beta chain repertoire analysis by fragment length analysis (spectratyping) using fluorescent primers to measure CDR3 length variability, while unable to provide the extreme high resolution of deep sequencing, can provide a global "snapshot" of T-cell receptor repertoire diversity, which is useful for most clinical applications where this level of assessment is required. It is important to note that this method uses PCR to amplify the rearranged variable regions to provide adequate template for sequencing (fragment length analysis), and this can introduce bias due to the more efficient amplification of certain templates compared to others. However, despite this limitation, since this assay is not quantitative, it is still able to provide an assessment of diversity by measuring the CDR3 length in various TCR V beta genes, which are organized into 24 families.

**Useful For:** Assessment of T-cell receptor diversity in various clinical contexts including primary immunodeficiencies, monitoring immune reconstitution posthematopoietic cell transplantation, and temporal assessment of repertoire changes in autoimmune diseases and viral infections

**Interpretation:** An interpretive report will be provided with adult and pediatric reference values for the relative contribution of each family to the total repertoire (% diversity ratio). The interpretation will be based on visual analysis of the spectratype (polyclonal, oligoclonal, or monoclonal) for each family as well as assessment of the number of peaks (numerical value not reported), and diversity ratio (DR) (reported value). Information on the distribution of peaks, eg, Gaussian vs non-Gaussian, will also be included in the report, where appropriate. Internal analytical and quality controls will be assessed to determine the suitability of reporting a patient result. Correlation with the clinical context will be made when possible, based on clinical history provided in the patient information sheet (which should be provided with the patient sample).

**Reference Values:** References values will be provided in the patient report.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Tea IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Tea, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to tea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
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</table>
Telomere Defects Gene Panel

Clinical Information: Telomeres are highly specialized structures composed of TTAGGG nucleotide repeats and proteins that protect chromosome ends. Under normal circumstances, telomeres shorten with every cycle of DNA replication. Telomerase is an enzyme complex that can extend the length of the telomere, thus helping to slow the shortening process. Telomerase is most active in highly proliferative tissues such as lymphocytes, skin, intestine, and bone marrow. Variants in genes involved with telomere repair and maintenance may cause telomeres to shorten more quickly than normal. Telomere biology disorders (TBD) are a complex group of bone marrow failure syndromes (BMFS) characterized by abnormally short telomeres. The severity of these syndromes is variable, and they may present in children or adults. In addition to bone marrow failure, other symptoms of telomere biology disorders include pulmonary fibrosis, liver disease, gastrointestinal disease, and mucocutaneous abnormalities. Recognition and diagnosis of underlying TBD is important as it can help guide treatment decisions. Dyskeratosis congenita (DC) was the first TBD to be described. The subsets of DC include classic DC, Hoyeraal Hreidarsson syndrome (HHS), Revesz syndrome, DC-like conditions and isolated subtypes. Patients with the classic forms of DC are usually diagnosed in childhood, and they have a triad of mucocutaneous features including dysplastic nails, anomalies of skin pigmentation, and oral leukoplakia. Other features of DC may include bone marrow failure, gastrointestinal disease, liver disease, pulmonary fibrosis, a predisposition to certain cancers, and other medical problems. Other TBDs presenting in childhood include HHS and Revesz syndrome. TBD may also manifest in adulthood and the presentation can be variable. A broad umbrella of conditions could include bone marrow failure, pulmonary fibrosis, liver disease not otherwise classified, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) or early onset of malignancies within the DC grouping. Telomere biology disorders can be inherited in a variety of patterns, including X-linked recessive, autosomal dominant, and autosomal recessive. At least 50% of patients with DC have mutations in the DKC1, TERC, TERT, TINF2, NHP2, and NOP10 genes. In autosomal dominant DC, phenotypes may present at a younger age and more severely in successive generations (genetic anticipation). See Table 1 for a summary of the genes included in this panel, associated diseases and the mode of inheritance. Alternatively, some patients may have 1 of these 3 features along with a hypocellular bone marrow. These patients all have very short telomeres (<1% percentile of age) in leukocytes. Patients with HHS have the features of classic DC but additionally have cerebellar hypoplasia. Telomere length analysis in leukocyte subsets is performed by flow-FISH (see references). They can also have low T cell numbers with severe B and NK cell lymphopenia (T+/B-NK-) reminiscent of severe combined immunodeficiency (SCID). In Revesz syndrome, patients have bilateral exudative retinopathy along with other features of DC. In patients who do not meet the diagnostic criteria of DC but have several features reminiscent of the disease, a classification of DC-like may be applied. This could include presence of bone marrow failure, developmental delay, familial history of pulmonary fibrosis, and no other clear diagnosis. These patients usually have short, but not very short telomeres, and may or may not have a genetic defect in one of the known telomere biology genes. However, these patients need careful monitoring as they may evolve into the more classic forms of DC over time. Individuals who have mutations in one of the telomere genes and have very short telomeres (<1% percentile of normal for age) who have a single feature of a telomere disorder or DC could be considered to be an isolated subtype. The stringency of monitoring depends on the individual case, age of patient, complications, and should include counseling for family members for potential disease risk and the phenomenon of genetic anticipation. Patients with aplastic anemia may have mutations in TERC, TERT, and TINF2 genes. Approximately 20% of patients with idiopathic pulmonary fibrosis (IPF) have a familial inheritance, which is autosomal dominant but with variable penetrance and approximately 30% of patients with familial IPF have short telomeres with genetic defects in the telomere genes. The genes most
commonly identified in the context of IPF are TERC and TERT. The telomerase complex includes a
reverse transcriptase encoded by TERT, RNA template (encoded by TERC), and associated other proteins
that regulate the assembly, trafficking, recruitment of telomerase to telomeres and stability of telomeres,
including dyskerin (DKC1). Other members of the telomerase complex include NOP10 (NOLA3) and
NHP2 (NOLA2). The shelterin complex, which is a 6-protein complex that coats telomeres and offers
telomere end protection. The shelterin complex directs telomere length homeostasis (T-loop) and prevents
DNA damage response activation. The DNA helicase, RTEL1 promotes telomere elongation through the
unwinding of the T-loop. TCAB1 (WRAP53) directs trafficking of the telomerase complex to the
telomeric ends. The CST complex of 3 proteins (CTC1 and others) inhibits telomerase activity and
promotes capping. Table 1. Genes included in the Telomere Defect PID Gene Panel GENE SYMBOL
(ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER CTC1 CST
complex subunit CTC1 613129 Approximately 1-3% of DC AR Cerebroretinal microangiopathy with
calcifications and cysts DKC1 H/ACA ribonucleoprotein complex subunit 4 isoform 1 300126
Approximately 17-36% of DC XL Dyskeratosis congenita NHP2 H/ACA ribonucleoprotein complex
subunit 2 isoform a 606470 <1% of DC AR Dyskeratosis congenita NOP10 H/ACA ribonucleoprotein
complex subunit 3 606471 <1% of DC AR Dyskeratosis congenita RTEL1 Regulator of telomere
elongation helicase 1 isoform 2 608833 Rare AR, AD Dyskeratosis congenita, pulmonary fibrosis and/or
bone marrow failure, TERC Telomerase RNA component 602322 Approximately 6-10% of DC AD
Dyskeratosis congenita, aplastic anemia, susceptibility to idiopathic pulmonary fibrosis TERT Telomerase
reverse transcriptase isoform 1 187270 Approximately 1-7% of DC AR,AD Dyskeratosis congenita, acute
myeloid leukemia, cutaneous melanoma, pulmonary fibrosis and/or bone marrow failure,
telomere-related TINF2 TERF1-interacting nuclear factor 2 isoform 1 604319 Approximately 11-24% of
DC AD Dyskeratosis congenita, Revesz syndrome USB1 (C16ORF57) U6 snRNA phosphodiesterase
isoform 1 613276 Rare AR Poikiloderma with neutropenia WRAP53 Telomerase Cajal body protein
1 (TCAB1) 612661 Approximately 3% of DC AR Dyskeratosis congenita

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family
history suggestive of telomeropathies Establishing a diagnosis of a telomeropathy, in some cases,
allowing for appropriate management and surveillance for disease features Identifying pathogenic
variants within genes known to be associated with increased risk for telomere defects allowing for
predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent
published American College of Medical Genetics and Genomics (ACMG) recommendations as a
guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported
with interpretive comments detailing their potential or known significance. Multiple in silico evaluation
tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in
silico evaluation tools is highly dependent upon the data available for a given gene, and predictions
made by these tools may change over time. Results from in silico evaluation tools should be interpreted
with caution and professional clinical judgment. Unless reported or predicted to cause disease,
alterations found deep in the intron or alterations that do not result in an amino acid substitution are not
reported. Information about these variants and common polymorphisms are available upon request. The
telomerase database is a useful tool for variant review and classification of telomere disorders that may
be used in some cases.

Reference Values:
An interpretive report will be provided.

Armanios MY, Chen JIL, Cogan JD, et al: Telomerase Mutations in Families with Idiopathic
Abraham RS, Aubert G: Flow cytometry, a versatile tool for diagnosis and monitoring of primary
Sarek G, Marzec P, Margalef P, Boulton SJ: Molecular basis of telomere dysfunction in human genetic
**Temazepam (Restoril), Serum**

**Reference Values:**
Reference Range: 50 - 1000 ng/mL

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**Terminal Deoxynucleotidyl Transferase (TdT) Immunostain, Technical Component Only**

**Clinical Information:** Terminal deoxynucleotidyl transferase (TdT) is a nuclear enzyme that adds individual nucleotides to the termini of DNA strands without the use of a DNA template. TdT is expressed normally in cortical thymocytes, immature hematopoietic stem cells, and B and T lymphoblasts. Diagnostically, TdT positivity can be helpful in confirming a diagnosis of lymphoblastic lymphoma or leukemia. Acute myeloid leukemias can also express TdT.

**Useful For:** Classification of leukemias or lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC/Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Kang LC, Dunphy CH: Immunoreactivity of MIC2 (CD99) and terminal deoxynucleotidyl transferase in bone marrow clot and core specimens of acute myeloid leukemias and myelodysplastic syndromes. Arch Pathol Lab Med 2006;130:153-157

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**TERT Promoter Analysis, Tumor**

**Clinical Information:** TERT gene encodes the catalytic subunit of telomerase, an enzyme complex that regulates telomere length. TERT promoter mutations in 2 hotspots (C228T and C250T) have been shown to increase telomerase activity and contribute to tumorigenesis by allowing cancer cells to overcome cellular senescence. Among central nervous system tumors, TERT promoter mutations have primarily been identified in adults, with highest frequencies in oligodendroglioma, primary glioblastoma, solitary fibrous tumor, and medulloblastoma. Although less frequent, TERT promoter mutations have also been observed in lower-grade infiltrating (diffuse and anaplastic) astrocytomas and ependymoma, and are rare or absent in other central nervous system tumor types. The presence of TERT promoter mutations have been associated with a less favorable prognosis in lower-grade (grade II/III) diffuse gliomas that lack IDH1/2 mutations and have intact 1p/19q ("IDH-wildtype astrocytomas"), and with a more favorable prognosis in prognosis in grade II/III IDH1/2-mutant and 1p/19q-codeleted diffuse gliomas ("IDH-mutant and 1p/19q codeleted oligodendrogliomas"). Assessment of TERT promoter mutation status in central nervous system tumors may assist in tumor classification and provide prognostically relevant information for subgroups of patients with lower-grade diffuse gliomas. TERT gene mutations are also observed in a variety of non-central nervous system (CNS) tumor types. In hepatocellular neoplasms TERT promoter mutations occur frequently in hepatocellular carcinomas and are believed to be an early step in hepatocarcinogenesis. However, TERT promoter mutations are not specific to hepatocellular carcinoma.
and have been reported as a key alteration in the rare progression of hepatocellular adenomas to hepatocellular carcinomas. As such, identification of a TERT promoter mutation suggests a hepatocellular neoplasm with an increased risk for aggressive behavior.

**Useful For:** Assisting in central nervous system tumor classification This test is not useful for hematological malignancies.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**Testosterone, Total and Bioavailable, Serum**

**Clinical Information:** Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone, with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which, in men, is also called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotropins by athletes. Decreased testosterone in females causes subtle
symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest but progressive decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism consequent to aging alone is rare.

Measurement of total testosterone (TTST / Testosterone, Total, Mass Spectrometry, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH (LH / Luteinizing Hormone [LH], Serum) and follicle stimulating hormone (FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particular if abnormalities in SHBG (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of bioavailable (this test) or free testosterone (TGRP / Testosterone, Total and Free, Serum) are recommended in this situation. While both bioavailable and free testosterone can be used for the same indications, determination of bioavailable testosterone levels may be superior to free testosterone measurement in most situations.

**Useful For:** Recommended second-level test for suspected increases or decreases in physiologically active testosterone: -Assessment of androgen status in cases with suspected or known sex hormone-binding globulin binding abnormalities -Assessment of functional circulating testosterone in early pubertal boys and older men -Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism but normal total testosterone levels -Monitoring of testosterone therapy or antiandrogen therapy in older men and in females

**Interpretation:** Total testosterone and general interpretation of testosterone abnormalities: In male patients: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXY males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, con genital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further work-up is necessary to determine the cause of precocious puberty. In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). In female patients: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia. Non-classical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17 hydroxyprogesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. -Analogous to males, but at lower levels in prepubertal girls, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms. High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic
ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance, and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly exceed 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, then levels should be kept within the normal female range at all times. Bioavailable (this test) or free testosterone (TGRP / Testosterone, Total and Free, Serum) levels should also be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable (this test) or free testosterone (TGRP / Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. Testosterone, Total and Bioavailable: Usually, bioavailable (and free testosterone) levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding. -Liver disease and severe systemic illness. -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. -Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (this test) or free testosterone (TGRP / Testosterone, Total and Free, Serum) should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. These men not only have elevated SHBG levels, but albumin levels may also vary, due to coexisting illnesses.

**Reference Values:**

**TESTOSTERONE, TOTAL**

**Males**

- 0-5 months: 75-400 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-130 ng/dL
- 12-13 years: <7-800 ng/dL
- 14 years: <7-1,200 ng/dL
- 15-16 years: 100-1,200 ng/dL
- 17-18 years: 300-1,200 ng/dL
- > or =19 years: 240-950 ng/dL

**Tanner Stages**

- I (prepubertal): <7-20
- II: 8-66
- III: 26-800
- IV: 85-1,200
- V (young adult): 300-950

**Females**

- 0-5 months: 20-80 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-44 ng/dL
- 12-16 years: <7-75 ng/dL
- 17-18 years: 20-75 ng/dL
- > or =19 years: 8-60 ng/dL

**Tanner Stages**

- I (prepubertal): <7-20
II: 7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

TESTOSTERONE, BIOAVAILABLE

Males
< or =19 years: not established
20-29 years: 83-257 ng/dL
30-39 years: 72-235 ng/dL
40-49 years: 61-213 ng/dL
50-59 years: 50-190 ng/dL
60-69 years: 40-168 ng/dL
> or =70 years: not established

Females (non-oophorectomized)
< or =19 years: not established
20-50 years (on oral estrogen): 0.8-4.0 ng/dL
20-50 years (not on oral estrogen): 0.8-10 ng/dL
>50 years: not established

Clinical References:

Testosterone, Total and Free, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which, in men, also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-menorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia); adrenal, testicular, and ovarian tumors; and abuse of testosterone or
gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest but progressive decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone (TTST / Testosterone, Total, Mass Spectrometry, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulating hormone (FSH) (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of free testosterone or bioavailable testosterone are recommended in this situation; bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) is the preferred assay. See Steroid Pathways in Special Instructions.

**Useful For:** Alternative, second-level test for suspected increases or decreases in physiologically active testosterone: -Assessment of androgen status in cases with suspected or known sex hormone-binding globulin-binding abnormalities -Assessment of functional circulating testosterone in early pubertal boys and older men -Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism, but normal total testosterone levels -Monitoring of testosterone therapy or antiandrogen therapy in older men and in females

**Interpretation:** Total testosterone and general interpretation of testosterone abnormalities: In male patients: Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXY males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels; causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition or excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the causes of precocious puberty. -In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). In female patients: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: non-classical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17-hydroxyprogesterone (OHPG / 17-Hydroxyprogesterone, Serum), often to a greater degree than testosterone. -Prepubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values
above 200 ng/dL. Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly above 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid over treatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate "idiopathic" female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. See Steroid Pathways in Special Instructions. Free testosterone: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa:

- Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding -Liver disease and severe systemic illness -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (this test) should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels, but albumin levels also may vary due to coexisting illnesses.

**Reference Values:**

**TESTOSTERONE, FREE**

Males (adult):

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25 years</td>
<td>5.25-20.7</td>
</tr>
<tr>
<td>25-30 years</td>
<td>5.05-19.8</td>
</tr>
<tr>
<td>30-35 years</td>
<td>4.85-19.0</td>
</tr>
<tr>
<td>35-40 years</td>
<td>4.65-18.1</td>
</tr>
<tr>
<td>40-45 years</td>
<td>4.46-17.1</td>
</tr>
<tr>
<td>45-50 years</td>
<td>4.26-16.4</td>
</tr>
<tr>
<td>50-55 years</td>
<td>4.06-15.6</td>
</tr>
<tr>
<td>55-60 years</td>
<td>3.87-14.7</td>
</tr>
<tr>
<td>60-65 years</td>
<td>3.67-13.9</td>
</tr>
<tr>
<td>65-70 years</td>
<td>3.47-13.0</td>
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<td>70-75 years</td>
<td>3.28-12.2</td>
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<tr>
<td>75-80 years</td>
<td>3.08-11.3</td>
</tr>
<tr>
<td>80-85 years</td>
<td>2.88-10.5</td>
</tr>
<tr>
<td>85-90 years</td>
<td>2.69-9.61</td>
</tr>
<tr>
<td>90-95 years</td>
<td>2.49-8.76</td>
</tr>
<tr>
<td>95-100+ years</td>
<td>2.29-7.91</td>
</tr>
</tbody>
</table>

Males (children):

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>Term infants</td>
</tr>
<tr>
<td>1-15 days</td>
<td>0.20-3.10</td>
</tr>
<tr>
<td>16 days-1 year</td>
<td>Values decrease gradually from newborn (0.20-3.10 ng/dL) to prepubertal levels</td>
</tr>
</tbody>
</table>

*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142*
### TESTOSTERONE, TOTAL

#### Males
- **0-5 months:** 75-400 ng/dL
- **6 months-9 years:** <7-20 ng/dL
- **10-11 years:** <7-130 ng/dL
- **12 years:** <7-20 ng/dL
- **13 years:** <0.04-0.34 ng/dL
- **14 years:** <0.04-0.59 ng/dL
- **15-18 years:** <0.04-0.84 ng/dL
- **19 years:** <0.04-1.06 ng/dL

#### Females (children):
- **<1 year:** Term infants
- **1-15 days:** 0.06-0.25 ng/dL
- **16 days-1 year:** Values decrease gradually from newborn (0.06-0.25 ng/dL) to prepubertal levels
  
  *Citation: J Clin Endocrinol Metab, 36(6):1132-1142, 1973

#### Females (adult):
- **20-<25 years:** 0.06-1.08 ng/dL
- **25-<30 years:** 0.06-1.06 ng/dL
- **30-<35 years:** 0.06-1.03 ng/dL
- **35-<40 years:** 0.06-1.00 ng/dL
- **40-<45 years:** 0.06-0.98 ng/dL
- **45-<50 years:** 0.06-0.95 ng/dL
- **50-<55 years:** 0.06-0.92 ng/dL
- **55-<60 years:** 0.06-0.90 ng/dL
- **60-<65 years:** 0.06-0.87 ng/dL
- **65-<70 years:** 0.06-0.84 ng/dL
- **70-<75 years:** 0.06-0.82 ng/dL
- **75-<80 years:** 0.06-0.79 ng/dL
- **80-<85 years:** 0.06-0.76 ng/dL
- **85-<90 years:** 0.06-0.73 ng/dL
- **90-<95 years:** 0.06-0.71 ng/dL
- **95-100+ years:** 0.06-0.68 ng/dL

### TESTOSTERONE, TOTAL

#### Females (children):
- **<1 year:** Term infants
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### Current as of June 14, 2021 12:13 pm CDT

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Tanner Stages*
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III: 26-800
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Tanner Stages*
I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

Clinical References:
4. Sizonenko PC, Paunier L: Hormonal changes in puberty III: Correlation of plasma dehydroepiandrosterone, testosterone, FSH and LH with stages of puberty and bone age in normal boys and girls and in patients with Addison's disease or hypogonadism or with premature or late adrenarche. J Clin Endocrinol Metab. 1975 Nov;41(5):894-904

Testosterone, Total, Bioavailable, and Free, Serum

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thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia); adrenal, testicular, and ovarian tumors; and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone (TTST / Testosterone, Total, Mass Spectrometry, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulation hormone (FSH) (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of free testosterone or bioavailable testosterone are recommended in this situation: bioavailable testosterone (see TTBS / Testosterone, Total and Bioavailable, Serum) is the preferred assay.

**Useful For:** Second- or third-order test for evaluating testosterone status (eg, when abnormalities of sex hormone-binding globulin are present)

**Interpretation:** Total testosterone and general interpretation of testosterone abnormalities: In male patients: Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXY males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels; causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition or excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause of precocious puberty -In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). In female patients: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: non-classical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17 hydroxyprogesterone (OHPG /
17-Hydroxyprogesterone, Serum), often to a greater degree than testosterone. -Prepubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values greater than 200 ng/dL. -Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form part of this syndrome. Total testosterone levels may be normal or mildly elevated and, uncommonly, greater than 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate "idiopathic" female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical endpoints and the primary treatment end point is the clinical response. Bioavailable and Free Testosterone: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the SHBG (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding. -Liver disease and severe systemic illness. -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable or free testosterone should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels, but albumin levels also may vary due to coexisting illnesses.

Reference Values:

**TESTOSTERONE, TOTAL**

**Males**
- 0-5 months: 75-400 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-130 ng/dL
- 12-13 years: <7-800 ng/dL
- 14 years: <7-1,200 ng/dL
- 15-16 years: 100-1,200 ng/dL
- 17-18 years: 300-1,200 ng/dL
- > or =19 years: 240-950 ng/dL

**Tanner Stages***
- I (prepubertal): <7-20
- II: 8-66
- III: 26-800
- IV: 85-1,200
- V (young adult): 300-950

**Females**
- 0-5 months: 20-80 ng/dL
- 6 months-9 years: <7-20 ng/dL
- 10-11 years: <7-44 ng/dL
- 12-16 years: <7-75 ng/dL
- 17-18 years: 20-75 ng/dL

*[Current as of June 14, 2021 12:13 pm CDT] 800-533-1710 or 507-266-5700 or mayocliniclabs.com ](http://mayocliniclabs.com) [Page 2436](http://mayocliniclabs.com)
> or =19 years: 8-60 ng/dL
Tanner Stages*
I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

TESTOSTERONE, FREE
Males (adult):
20-<25 years: 5.25-20.7 ng/dL
25-<30 years: 5.05-19.8 ng/dL
30-<35 years: 4.85-19.0 ng/dL
35-<40 years: 4.65-18.1 ng/dL
40-<45 years: 4.46-17.1 ng/dL
45-<50 years: 4.26-16.4 ng/dL
50-<55 years: 4.06-15.6 ng/dL
55-<60 years: 3.87-14.7 ng/dL
60-<65 years: 3.67-13.9 ng/dL
65-<70 years: 3.47-13.0 ng/dL
70-<75 years: 3.28-12.2 ng/dL
75-<80 years: 3.08-11.3 ng/dL
80-<85 years: 2.88-10.5 ng/dL
85-<90 years: 2.69-9.61 ng/dL
90-<95 years: 2.49-8.76 ng/dL
95-100+ years: 2.29-7.91 ng/dL

Males (children):
<1 year: Term infants
1-15 days: 0.20-3.10 ng/dL
16 days-1 year: Values decrease gradually from newborn (0.20-3.10 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-8 years: <0.04-0.11 ng/dL
9 years: <0.04-0.45 ng/dL
10 years: <0.04-1.26 ng/dL
11 years: <0.04-5.52 ng/dL
12 years: <0.04-9.28 ng/dL
13 years: <0.04-12.6 ng/dL
14 years: 0.48-15.3 ng/dL
15 years: 1.62-17.7 ng/dL
16 years: 2.93-19.5 ng/dL
17 years: 4.28-20.9 ng/dL
18 years: 5.40-21.8 ng/dL
19 years: 5.36-21.2 ng/dL

Females (adult):
20-<25 years: 0.06-1.08 ng/dL
25-<30 years: 0.06-1.06 ng/dL
30-<35 years: 0.06-1.03 ng/dL
35-<40 years: 0.06-1.00 ng/dL
40-<45 years: 0.06-0.98 ng/dL
45-<50 years: 0.06-0.95 ng/dL
50-<55 years: 0.06-0.92 ng/dL
55-<60 years: 0.06-0.90 ng/dL
60-<65 years: 0.06-0.87 ng/dL
65-<70 years: 0.06-0.84 ng/dL
70-<75 years: 0.06-0.82 ng/dL
75-<80 years: 0.06-0.79 ng/dL
80-<85 years: 0.06-0.76 ng/dL
85-<90 years: 0.06-0.73 ng/dL
90-<95 years: 0.06-0.71 ng/dL
95-100+ years: 0.06-0.68 ng/dL

Females (children):
<1 year: Term infants
1-15 days: 0.06-0.25 ng/dL*
16 days-1 year: Values decrease gradually from newborn (0.06-0.25 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-4 years: <0.04 ng/dL
5 years: <0.04-0.07 ng/dL
6 years: <0.04-0.14 ng/dL
7 years: <0.04-0.23 ng/dL
8 years: <0.04-0.34 ng/dL
9 years: <0.04-0.46 ng/dL
10 years: <0.04-0.59 ng/dL
11 years: <0.04-0.72 ng/dL
12 years: <0.04-0.84 ng/dL
13 years: <0.04-0.96 ng/dL
14 years: <0.04-1.06 ng/dL
15-18 years: <0.04-1.09 ng/dL
19 years: 0.06-1.08 ng/dL

TESTOSTERONE, BIOAVAILABLE
Males
< or =19 years: not established
20-29 years: 83-257 ng/dL
30-39 years: 72-235 ng/dL
40-49 years: 61-213 ng/dL
50-59 years: 50-190 ng/dL
60-69 years: 40-168 ng/dL
> or =70 years: not established

Females (non-oophorectomized)
< or =19 years: not established
20-50 years (on oral estrogen): 0.8-4.0 ng/dL
20-50 years (not on oral estrogen): 0.8-10 ng/dL
>50 Years: not established

Testosterone, Total, Mass Spectrometry, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it exerts anabolic effects and influences behavior. In males, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenal glands and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which, in males, is also called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligomenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in men but can cause distressing symptoms in females. The exact cause for mild-to-moderate elevations of testosterone often remains obscure. Common causes of pronounced elevations include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult males, there also is a gradual modest but progressive decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare.

Measurement of total testosterone is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulating hormone (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone Total and Free, Serum) are recommended in this situation. See Steroid Pathways in Special Instructions.

Useful For: Evaluation of men with symptoms or signs of possible hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, osteoporosis, or infertility Evaluation of boys with delayed or precocious puberty Monitoring testosterone replacement therapy Monitoring antiandrogen therapy (eg, used in prostate cancer, precocious puberty, treatment of idiopathic hirsutism, male-to-female transgender disorders, etc.) Evaluation of women with hirsutism, virilization, and oligoamenorrhea Evaluation of women with symptoms or signs of possible testosterone deficiency Evaluation of infants with ambiguous genitalia or virilization Diagnosis of androgen-secreting tumors

Interpretation: In males: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXY males) -Developmental causes (eg, testicular maldevelopment) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders
Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal" LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause of precocious puberty. -In adult males, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value, typically <50% ng/dL). In females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia. Non-classical (mild) variants may not present in childhood, but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17 hydroxyprogesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. -Analogous to males, but at lower levels in prepubertal girls, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms. High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly above 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, then levels should be kept within the normal female range at all times. Bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) levels should also be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. See Steroid Pathways in Special Instructions.

Reference Values:

Males
0-5 months: 75-400 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-130 ng/dL
12-13 years: <7-800 ng/dL
14 years: <7-1,200 ng/dL
15-16 years: 100-1,200 ng/dL
17-18 years: 300-1,200 ng/dL
> or =19 years: 240-950 ng/dL
Tanner Stages*
I (prepubertal): <7-20
II: 8-66
III: 26-800
IV: 85-1,200
V (young adult): 300-950

Females
0-5 months: 20-80 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-44 ng/dL
12-16 years: <7-75 ng/dL
17-18 years: 20-75 ng/dL
> or =19 years: 8-60 ng/dL

Tanner Stages*
I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References:

**Tetanus Toxoid IgG Antibody, Serum**

**Clinical Information:** Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin, tetanospasmin. Tetanospasmin attaches to peripheral nerve endings and travels to the central nervous system (CNS) where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospasmin), which stimulates development of antitetanus toxoid antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. Two to 3 weeks following vaccination, a patient's immunological response may be assessed by measuring the total antitetanus toxoid IgG antibody level in serum. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

**Useful For:** Assessment of an antibody response to the tetanus toxoid vaccine, which should be performed at least 3 weeks after immunization An aid to diagnose immunodeficiency

**Interpretation:** Results greater than or equal to 0.01 suggest a vaccine response. A tetanus toxoid booster should strongly be considered for patients with anti-tetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients who have a measurable serum level of 0.01 to 1.0 IU/mL.
TTOX
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Tetanus Toxoid, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to tetanus toxoid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
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<th>Class</th>
<th>IgE kU/L</th>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.

Tetrahydrobiopterin and Neopterin Profile (BH4, N)

**Clinical Information:** CSF Neopterin/Tetrahydrobiopterin (NC03) is useful for diagnosis of certain disorders of neurotransmitter metabolism. This testing may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL Tetrahydrobiopterin (BH4) serves as a cofactor for the hydroxylation of phenylalanine and in the biosynthesis of biogenic amines. Deficiency of BH4 may occur as a result of mutations causing a reduction in one of the three biosynthetic enzymes, guanosine triphosphate cyclohydrolase, 6-pyruvoyl-tetrahydropterin synthase, sepiapterin reductase, or the two regenerating enzymes, pterin-4-carbinolamine dehydratase, and dihydropteridine reductase. Defects in BH4 metabolism can result in hyperphenylalaninemia and deficiency of the neurotransmitters dopamine and serotonin. Changes in CSF neopterin may also occur in deficiency of the BH4 synthesis pathway. Disorders of BH4 metabolism are characterized by a wide range of symptoms that may include developmental delay, mental disability, behavioral disturbances, dystonia, Parkinsonian symptoms, gait disturbances, speech delay, psychomotor retardation and ptosis.

**Reference Values:**

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<tr>
<td>(years)</td>
<td>(nmol/L)</td>
<td>(nmol/L)</td>
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</tr>
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<td>Adults</td>
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<td>8 - 28</td>
</tr>
</tbody>
</table>

**Note:** If test results are consistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing. An important consideration for false positive for false negative results is the improper labeling of the patient sample.

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Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

**Clinical Information:** This consultative study is primarily designed for the evaluation of microcytosis but also has the ability to test for the detection of almost all known hemoglobin disorders in an economical manner. Because this can include multiple tests for alpha-thalassemias, beta-thalassemias, delta-beta-thalassemia, hereditary persistence of fetal hemoglobin (HPFH), and for all known hemoglobin (Hb) variants, an expert in these disorders can guide testing to explain the clinical question or reported complete blood cell count values. This evaluation is particularly useful for complete classification of compound combinations of Hb S with alpha- or beta-thalassemia, Hb...
E/beta-0-thalassemia, and many other complex alpha and beta thalassemia disorders. Since iron deficiency can mimic thalassemias, ferritin levels are measured to evaluate this possibility, if a serum sample is received. Hb disorders include those associated with thalassemias (decreased protein quantity) and Hb variants (abnormal protein production). Many are clinically harmless and others cause symptoms including microcytosis, sickling disorders, hemolysis, erythrocytosis, cyanosis/hypoxia, long-standing or familial anemia, compensated or episodic anemia, and increased methemoglobin or sulfhemoglobin results. Hb disorders can show patterns of either autosomal recessive or autosomal dominant inheritance. The thalassemias are a group of disorders of Hb synthesis. Normal adult Hb consists of 2 alpha globin chains (encoded by 2 pairs of alpha globin genes, each pair located on chromosome 16), and 2 beta globin chains (encoded by 2 beta globin genes, each located on chromosome 11). Thalassemia syndromes result from an underproduction of 1 or 2 types of globin chains and are characterized by the type (alpha, beta, delta, gamma) and magnitude of underproduction (number of defective genes) and the severity of clinical symptoms (minor, intermedia, major). The severity of the clinical and hematologic effects is directly related to the imbalance of alpha-like to beta-like chains. The most common form of thalassemia is alpha thalassemia. Alpha thalassemia usually involves deletion of entire alpha genes, and varies in severity depending on the number of alpha chains deleted (or rendered nonfunctional). Alpha thalassemia trait usually results from the deletion of two alpha genes. The most common form of Hb H disease, results from dysfunction of 3 alpha chains, and shows a variable phenotype with most showing moderate anemia. The deletion of all 4 alpha genes (Barts hydrops fetalis) is incompatible with life without significant medical intervention. Non-deletional alpha thalassemia alterations can also result in either thalassemia trait or Hb H disease and are less common than deletional forms. Conversely most beta thalassemia alterations are due to single nucleotide substitutions that can occur anywhere in the beta globin gene. Large deletions of the beta globin gene complex can result in elevations in Hb F, such as hereditary persistence of fetal hemoglobin (HPFH) or delta-beta thalassemia. While the presence of a single beta gene variants (beta thalassemia trait) results primarily in red blood cells (RBC) microcytosis, cases with two beta gene abnormalities show a wide range in clinical severity, and many cases require molecular testing to understand the phenotype.

Useful For: Evaluation of microcytosis Extensive and economical diagnosis and classification of hemoglobinopathies or thalassemia including complex disorders Diagnosis of hereditary persistence of hemoglobin (HPFH)

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Definitive results and an interpretive report will be provided.


THEV0 608092

Thalassemia Summary Interpretation, Blood

Clinical Information: Some hemoglobin disorders can be very complex and involve abnormalities of the alpha, beta, delta, and gamma genes. These abnormalities can be due to, not only to point variants, but also deletions within 1 or more globin genes. Multiple genetic variants can be seen in the same patient, and molecular testing is necessary to fully evaluate such cases. A summary interpretation that incorporates all of the testing performed is beneficial to the ordering physician.

Useful For: Incorporating and summarizing subsequent molecular results into an overall evaluation if 1 or more molecular tests are reflexed on the THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood
**Interpretation:** An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

**Reference Values:**
Only orderable as a reflex. For more information see THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood.

An interpretive report will be provided.

**Clinical References:**

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**TLU 8603**

**Thallium, 24 Hour, Urine**

**Clinical Information:** Thallium is odorless and tasteless and is found in trace amounts in the earth's crust. It is used in the manufacturing of electronic devices, switches, and closures. It had previously been used in rodenticides. The greatest exposure can occur from eating food (eg fruits and vegetables) since its easily taken up by plants through the roots. Cigarette smoking is also a source of exposure. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 gram. Most thallium is excreted in the urine and can be found within an hour after exposure and be detected as long as two months after exposure.

**Useful For:** Detecting toxic thallium exposure in 24-hour urine specimens

**Interpretation:** Patients exposed to high doses of thallium (>1 g) present with alopecia, peripheral neuropathy, seizures, and renal failure. Exposed patients can have urine output greater than 10 mcg/day. The long-term consequences of such an exposure are poor.

**Reference Values:**
0-17 years: not established
> or =18 years: <2 mcg/24 hours

**Clinical References:**
5. Rafai N, Horvath AR, Wittwer CT: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

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**TLB 8149**

**Thallium, Blood**

**Clinical Information:** Thallium is odorless and tasteless and is found in trace amounts in the earth's crust. It is used in the manufacturing of electronic devices, switches, and closures. It had previously...
been used in rodenticides. The greatest exposure can occur from eating food (eg, fruits and vegetables) since it's easily taken up by plants through the roots. Cigarette smoking is also a source of exposure. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 gram. Most thallium is excreted in the urine and can be found within an hour after exposure and be detected as long as two months after exposure.

**Useful For:** Detecting toxic thallium exposure in whole blood specimens

**Interpretation:** Normal blood concentrations are less than 1 ng/mL. Significant exposure is associated with thallium concentrations in blood greater than 10 ng/mL, and as high as 50 ng/mL. The long-term sequelae from such an exposure is poor. Patients exposed to high doses of thallium (>1 g) present with alopecia (hair loss), peripheral neuropathy, seizures, and renal failure.

**Reference Values:**

0-17 years: not established  
> or =18 years: <2 ng/mL


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**TLCRU 60325**

**Thallium/Creatinine Ratio, Random, Urine**

**Clinical Information:** Thallium is found in some depilatories and rodenticides. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 gram.

**Useful For:** Detecting toxic thallium exposure in random urine specimens

**Interpretation:** Patients exposed to high doses of thallium (>1 g) present with alopecia, peripheral neuropathy and seizures, and renal failure. Normal daily output is less than 1 mcg/day. Exposed patients can have urine output greater than 10 mcg/day. The long-term consequences of such an exposure are poor.

**Reference Values:**

0-17 years: not established  
> or =18 years: <2 mcg/g creatinine


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**THBNG 64872**

**THBD Gene, Next-Generation Sequencing, Varies**

**Clinical Information:** Thrombomodulin (TM) is an endothelial cell membrane protein found mainly in capillary beds that functions as a co-factor to thrombin in the activation of protein C. TM binds to thrombin and switches its substrate specificity from procoagulant substrates fibrinogen, factor V, factor VIII, and platelets to antiocoagulant protein C, enhancing activation by 1000-fold. Activated protein C downregulates further thrombin generation, suppressing clot formation. TM also has an anti-inflammatory role as a negative regulator of the complement arm of the innate immune system. TM enhances activation of thrombin activatable fibrinolysis inhibitor (TAFI, also known as procarboxypeptidase B), which inhibits fibrinolysis and inactivates complement-derived anaphalatoxins C3a and C5a. TM, in a
thrombin-independent manner, also interferes with inflammation by suppressing leukocyte trafficking and dampening complement activation through lectin-like domain (4). Despite its role in coagulation, it is unclear whether thrombomodulin gene alterations play a significant role in venous thromboembolism (5). The THBD gene encodes thrombomodulin and pathogenic alterations in the gene appear rare among thrombophilic patients, even those with severe thrombophilia (4). No severe TM deficiencies have been identified in patients with thrombosis, indicating that thrombomodulin alterations, in the absence of protein C deficiency, might not be associated with large vessel thrombosis (5). Since strong genotype-phenotype correlation has yet to be demonstrated between these alterations and venous thrombosis, indiscriminate testing for alterations in THBD or other genes related to coagulation in unselected patients presenting with a first episode of venous thrombosis is not recommended. A set of clinical guidelines from the British Society for Haematology on testing for heritable thrombophilia (1) is freely available. There is somewhat stronger evidence of an association between thrombomodulin gene polymorphisms and a moderately increased risk for arterial thrombosis, although more studies including a larger number of patients are needed to more firmly establish this risk (5). Some alterations in THBD are associated with atypical hemolytic uremic syndrome (aHUS), which is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. An estimated 5% of patients with aHUS have alterations in THBD (4). However, it appears that an alteration of a single THBD allele is not sufficient by itself to cause aHUS and additional factors are probably required, such as virus-like illness (4). A method to screen patients of aHUS based on presentation and a recommended list of investigations has been developed by The European Paediatric Study Group for HUS (3). Finally, a specific alteration in THBD, c.1611C>A (p.Cys537*), is associated with an autosomal dominant hereditary bleeding disorder characterized by excessive bleeding following physical trauma or surgery and extremely elevated levels of soluble TM (6,7,8). As of January 2019, this is the only alteration in THBD associated with a bleeding disorder reported in the Human Gene Mutation Database (HGMD Professional 2018.4). A systematic diagnosis through conventional coagulation testing is recommended prior to considering genetic testing for any suspected bleeding disorder. THBD-related bleeding is associated with normal results for these tests (i.e., normal prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen assays) (7). Individuals with THBD-related bleeding have been observed to have normal results for the following assays as well: Coagulation factors II, V, VII, VIII, IX, X, XI, XII, and XIII, von Willebrand factor antigen, von Willebrand cofactor activity, plasma antithrombin, protein C and S levels, and activated protein C ratio (7). Additionally, there should be no evidence of platelet dysfunction. In individuals with THBD-related bleeding, prothrombin consumption index has been observed to be elevated (7) and levels of soluble TM are extremely elevated (6). If an assessment of thrombin generation and measurement of plasma TM levels finds reduced thrombin generation or there are extremely high levels of soluble TM and no other explanation for bleeding can be found, a diagnosis of THBD-related bleeding should be considered and molecular testing is clinically indicated (7,9).

**Useful For:**

- Ascertaining a pathogenic alteration in the THBD gene in patients with atypical hemolytic uremic syndrome
- Ascertaining a pathogenic alteration in the THBD gene in patients with reduced thrombin generation and a strong family or personal history of excessive bleeding that is not explained by results of conventional and specialized coagulation testing
- This test is not intended for prenatal diagnosis

**Interpretation:**

An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


**FFTCC**

**THC Confirmation, MS, SP**

**Interpretation:** Assay threshold: 1.0 ng/mL

**Reference Values:**

Negative

Units: ng/mL

Test Performed by: Medtox Laboratories, Inc.
402 W. County Road D
St. Paul, MN 55112

**THEO**

**Theophylline, Serum**

**Clinical Information:** Theophylline and its congener, aminophylline, are used to relax smooth muscles of the bronchial airways and pulmonary blood vessels to relieve and prevent symptoms of asthma and bronchospasm. Theophylline is typically administered orally at a dose of 400 mg/day or 6 mg/kg, whichever is lower, or intravenously as aminophylline at 0.4 mg/kg/hour. Oral dosage may be increased at 200-mg increments to a maximum of 900 mg/day, or 13 mg/kg if the steady-state blood concentration is within the therapeutic range of 8.0 to 20.0 mcg/mL. Theophylline has a half-life of approximately 4 hours in children and adult smokers, and 8.7 hours in nonsmoking adults. The volume of distribution is approximately 0.5 L/kg, and the drug is approximately 40% protein bound. Theophylline exhibits zero-order clearance kinetics like phenytoin, small increases in dose yield disproportionately large increases in blood concentration. Coadministration of cimetidine and erythromycin will significantly inhibit theophylline clearance, requiring dosage reduction. Other drugs such as allopurinol, ciprofloxacin, oral contraceptives, and propranolol inhibit theophylline clearance to a lesser degree. Smoking induces the synthesis of cytochrome P448, the antipyrine-dependent cytochrome, which significantly increases the rate of metabolism of theophylline. Drugs such as phenobarbital, phenytoin, carbamazepine, and rifampin slightly increase the rate at which the drug is cleared. Theophylline exhibits rather severe toxicity that is proportional to blood level.

**Useful For:** Assessing and adjusting theophylline dosage for optimal therapeutic level Assessing theophylline toxicity

**Interpretation:** Response to theophylline is directly proportional to the serum level. Patients usually...
receive the best response when the serum level is above 8.0 mcg/mL, with minimal toxicity experienced as long as the level is less than or equal to 20.0 mcg/mL.

**Reference Values:**
**Therapeutic:**
- Bronchodilation: 8.0-20.0 mcg/mL
- Neonatal apnea (< or =4 weeks old): 6.0-13.0 mcg/mL
- Critical value: >20.0 mcg/mL


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**Thermoactinomyces vulgaris, IgG Antibodies, Serum**

**Clinical Information:** Thermoactinomyces vulgaris is one of the causative agents of hypersensitivity pneumonitis (HP). Other causative microorganisms include Microsporidia faeni and Aspergillus fumigatus. The development of HP caused by Thermoactinomyces vulgaris is accompanied by an immune response to Thermoactinomyces vulgaris antigens with production of IgG antibodies. While the immunopathogenesis of HP is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.(1)

**Useful For:** Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Thermoactinomyces vulgaris

**Interpretation:** Elevated concentrations of IgG antibodies to Thermoactinomyces vulgaris, Aspergillus fumigatus, or Microsporidia faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**
- 0-12 years: < or =6.6 mg/L
- 13-18 years: < or =11.0 mg/L
- >18 years: < or =23.9 mg/L


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**Thiamine (Vitamin B1), Whole Blood**

**Clinical Information:** Thiamine (vitamin B1, thiamin) is an essential vitamin required for carbohydrate metabolism, brain function, and peripheral nerve myelination. Thiamine is obtained from the diet. Body stores are limited and deficiencies can develop quickly. The total thiamine pool in the average adult is about 30 mg. An intake of 0.5 mg per 1,000 kcal per day is needed to maintain this pool. Due to its relatively short storage time, marginal deficiency can occur within 10 days and more severe deficiency within 21 days if intake is restricted. Approximately 80% of all chronic alcoholics are thiamine deficient due to poor nutrition. However, deficiency also can occur in individuals who are elderly, have chronic gastrointestinal problems, have marked anorexia, are on cancer treatment, or are receiving diuretic therapy. The signs and symptoms of mild-to-moderate thiamine deficiency are nonspecific and may include poor sleep, malaise, weight loss, irritability, and confusion. Newborns breast fed from deficient mothers may develop dyspnea and cyanosis; diarrhea, vomiting, and aphonia may follow. Moderate deficiency can affect intellectual performance and well-being, despite a lack of apparent clinical symptoms. Severe deficiency causes congestive heart failure (wet beriberi), peripheral neuropathy (dry beriberi), Wernicke encephalopathy (a medical emergency that can progress to coma
and death), and Korsakoff syndrome (an often irreversible memory loss and dementia that can follow). Rapid treatment of Wernicke encephalopathy with thiamine can prevent Korsakoff syndrome. Symptoms of dry beriberi include poor appetite, fatigue, and peripheral neuritis. Symptoms of wet beriberi include cardiac failure and edema. Patients with Wernicke encephalopathy present with behavior change (confusion, delirium, apathy), diplopia (often sixth nerve palsies), and ataxia. A late stage, in which the patients may develop an irreversible amnestic confabulatory state, is referred to as the Wernicke-Korsakoff syndrome. The response to thiamine therapy in deficient patients is usually rapid. Thiamine deficiency is a treatable, yet underdiagnosed, disorder in the United States. A heightened level of awareness of the possibility of thiamine deficiency is necessary to identify, intervene, and prevent thiamine deficiency's dire consequences. It appears that no conditions are directly attributable to thiamine excess and that thiamine administration is safe except in extremely rare cases of anaphylaxis from intravenous thiamin. Whole blood thiamine testing is superior to currently available alternative tests for assessing thiamine status. Serum or plasma thiamine testing suffers from poor sensitivity and specificity, and less than 10% of blood thiamine is contained in plasma. Transketolase determination, once considered the most reliable means of assessing thiamine status, is now considered an inadequate method. The transketolase method is an indirect assessment. Since transketolase activity requires thiamin, decreased transketolase activity is presumed to be due to the decrease of thiamin. However, the test is somewhat nonspecific, as other factors may decrease transketolase activity. Transketolase is less sensitive than liquid chromatography-tandem mass spectrometry (LC-MS/MS), has poor precision, and specimen stability concerns.

Useful For: Assessment of thiamine deficiency Measuring thiamine levels in patients with behavioral changes, eye signs, gait disturbances, delirium, and encephalopathy; or in patients with questionable nutritional status, especially those who appear at risk and who also are being given insulin for hyperglycemia

Interpretation: Values for thiamine diphosphate of less than 70 nmol/L are suggestive of thiamine deficiency.

Reference Values:
70-180 nmol/L


Thiocyanate, Serum
Reference Values:
Toxic Thiocyanate concentrations: Greater than 10 mg/dL

Thiopurine Metabolites, Whole Blood
Clinical Information: This test is primarily used to verify compliance, optimize therapy, and identify elevated metabolite concentrations that may result in toxicity after initiation of thiopurine drug therapy for the treatment of inflammatory bowel disease. Recommended time points for monitoring include: 4 weeks after starting treatment to verify patient compliance and look for early risk of toxicity; 12 to 16 weeks after starting therapy when 6-thioguanine nucleotides have reached steady-state; and annually.(1) It may also be ordered in patients who do not respond to therapy as expected or as needed for dose changes, flare-ups, signs of toxicity, or suspicion of noncompliance. The test will measure 6-methylmercaptopurine
(6-MMP) and 6-thioguanine nucleotides (6-TGN) in erythrocytes.

**Useful For:** Aids physicians in dose adjustments, minimizing dose-dependent toxicity, and monitoring compliance of thiopurine drug therapy

**Interpretation:** Target 6-thioguanine (6-TGN) concentrations are 235 to 450 pmol/8x10^8 RBC with lower levels suggesting suboptimal dosing and higher levels associated with increased risk of myelotoxicity and leukopenia. High 6-methylmercaptopurine (6-MMP) levels (greater than 5700 pmol/8x10^8 RBC) suggest an increased risk for hepatotoxicity and potentially "thiopurine hypermethylation."

**Reference Values:**
- 6-Thioguanine Nucleotides (6-TGN): 235-450 pmol/8x10^8 RBC
- 6-Methylmercaptopurine (6-MMP): Less than or equal to 5700 pmol/8x10^8 RBC

**Clinical References:**

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**Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping, Varies**

**Clinical Information:** The thiopurine drugs are purine antimetabolites that are useful in the treatment of acute lymphoblastic leukemia, autoimmune disorders (eg, Crohn disease, rheumatoid arthritis), and organ transplant recipients. The thiopurine drugs, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), and azathioprine (AZA) are prodrugs that require intracellular activation to 6-thioguanine nucleotides (6-TGN). This activation is catalyzed by multiple enzymes. The cytotoxic effects of thiopurine drugs are achieved mainly through incorporation of 6-TGN into DNA and RNA. The pathway that leads to synthesis of active cytotoxic 6-TGN is in competition with inactivation pathways catalyzed by thiopurine methyltransferase (TPMT). Evaluation of this pathway is important because the level of 6-TGN measured in red blood cells have been correlated with both thiopurine therapeutic efficacy and toxicity such as myelosuppression. TPMT activity is inherited as a monogenic codominant trait, and variable TPMT activity is associated with TPMT genetic variants. The distribution of TPMT activity in red blood cells is trimodal in the white population, with approximately 0.3% of people having deficient (undetectable) TPMT activity, 11% low (intermediate) activity, and 89% normal TPMT activity. The allele for normal TPMT activity (wild type) has been designated TPMT*1. Four TPMT alleles, comprised of a combination of three different single-nucleotide variants (SNV), account for the majority of inactivating alleles in some ethnicities, including whites: TPMT*2, TPMT*3A, and TPMT*3C. Less frequently occurring TPMT alleles TPMT*4, TPMT*5, TPMT*8, and TPMT*12 also have been implicated as deficiency alleles. If no TPMT variant alleles are detected by this assay, the most likely genotype is that of TPMT*1/*1 although the presence of other rarer alleles cannot be excluded. Nudix hydrolase (NUDT15) is thought to dephosphorylate the active metabolites of thiopurines, TGTP and TdGTP, which prevents their incorporation into DNA and decreases their cytotoxic effects. Genetic variants in NUDT15 that decrease this activity are strongly associated with thiopurine-related myelosuppression. NUDT15 deficiency is most common among East Asian (22.6%), South Asian (13.6%), and Native American populations (12.5%-21.2%). Studies in other populations are ongoing. This test evaluates variants associated with NUDT15*2, NUDT15*3, NUDT15*4, and NUDT15*5. If no NUDT15 variant alleles are detected by this assay, the most likely genotype is that of NUDT15*1/*1 although the presence of other rarer alleles cannot be excluded. Individuals with variants in both TPMT and NUDT15 have been identified and were significantly more
sensitive to mercaptopurine than individuals heterozygous for a variant in only one gene. Integration of both TPMT and NUDT15 testing may allow for more accurate prediction of thiopurine-related toxicity risk to guide dosing, particularly among patients from diverse populations. TPMT allele cDNA nucleotide change (NM_000367.4) Amino acid change Effect on enzyme metabolism
*1 None (wild type) None (wild type) Normal function
*2 c.238G>C p.Ala80Pro (p.A80P) No activity
*3A c.460G>A and c.719A>G p.Ala154Thr (p.A154T) and p.Tyr240Cys (p.Y240C) No activity
*3B c.460G>A p.Ala154Thr (p.A154T) No activity
*3C c.719A>G p.Tyr240Cys (p.Y240C) No activity
*4 c.626-1G>A Not applicable, splice site No activity
*5 c.146T>C p.Leu49Ser (p.L49S) No activity
*12 c.374C>T p.Ser125Leu (p.S125L) Reduced activity

NUDT15 allele cDNA nucleotide change (NM_018283.3) Amino acid change Effect on enzyme metabolism
*1 None (wild type) None (wild type) Normal activity
*2 or *3 c.415C>T p.Arg139Cys (p.R139C) No activity
*4 c.416G>A p.Arg139His (p.R139H) No activity
*5 c.52G>A p.Val18Ile (p.V18I) No activity

The US Food and Drug Administration, the Clinical Pharmacogenetics Implementation Consortium, and some professional societies recommend consideration of TPMT and NUDT15 genotype testing or TPMT enzyme activity testing along with NUDT15 genotype testing prior to the initiation of therapy with thiopurine drugs. There is substantial evidence linking TPMT and NUDT15 genotype to phenotypic variability. Dose adjustments based upon TPMT and NUDT15 genotype have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings. Genotyping is not impacted by other medications known to inhibit TPMT activity. Complementary clinical testing is available to measure TPMT enzymatic activity in erythrocytes (TPMT3 / Thiopurine Methyltransferase Activity Profile, Erythrocytes) if the clinician wants to check for lower TPMT enzyme activity, regardless of cause. Testing for TPMT enzyme activity is not impacted by variants in NUDT15.

**Useful For:** Predicting potential for toxicity to thiopurine drugs (6-mercaptopurine, 6-thioguanine, and azathioprine)

**Interpretation:** An interpretive report will be provided. The TPMT genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the TPMT Nomenclature Committee.(1) NUDT15 genotype and associated star alleles are as described by Moriyama et al.(2) and catalogued in the Pharmacogene Variation Consortium (www.pharmvar.org). For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Thiopurine Methyltransferase Activity Profile, Erythrocytes**

**Clinical Information:** Thiopurine methyltransferase (TPMT) deficiency is a condition in which patients treated with standard doses of azathioprine (AZA, Imuran), 6-mercaptopurine (6-MP, Purinethol), or 6-thioguanine (6-TG, Thioguanine Tabloid) may develop life-threatening myelosuppression or severe...
hematopoietic toxicity. The metabolic conversion of AZA, 6-MP, or 6-TG to purine nucleotides and the subsequent incorporation of these nucleotides into DNA play an important role in both the therapeutic efficacy and the toxicity of these drugs. A competitive catabolic route for the metabolism of thiopurines is catalyzed by the TPMT enzyme, which inactivates them by thiomethylation. A balance must be established between these competing metabolic pathways so that: 1) sufficient amounts of drug are converted to the nucleotide to act as an antimetabolite and 2) the antimetabolite levels do not become so high as to cause potentially lethal bone marrow suppression. TPMT deficiency is an autosomal recessive condition with an incidence of approximately 1 in 300 individuals homozygous for deleterious mutations in the TPMT gene; about 10% of the population are heterozygous carriers of TPMT mutations. Adverse effects of AZA, 6-MP, or 6-TG administration can be observed in individuals who are either homozygous or heterozygous for TPMT deficiency. TPMT hyperactivity is also a known phenotype. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs, and therefore they cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity. Therefore, treatment with alternative medications is recommended for hypermetabolizers. As such, knowing a patient's TPMT status prior to treatment with AZA, 6-MP, or 6-TG is important for purposes of calculating drug dosages.

**Useful For:** Detection of individuals with low thiopurine methyltransferase (TPMT) activity who are at risk for excessive myelosuppression or severe hematopoietic toxicity when taking thiopurine drugs Detection of individuals with hyperactive TPMT activity who have therapeutic resistance to thiopurine drugs and may develop hepatotoxicity if treated with these drugs

**Interpretation:** This assay is used to detect individuals with low and intermediate thiopurine methyltransferase (TPMT) activity who may be at risk for myelosuppression when exposed to standard doses of thiopurines, including azathioprine (AZA, Imuran), 6-mercaptopurine (Purinethol), or 6-thioguanine (6-TG, Thioguanine Tabloid). TPMT is the primary metabolic route for inactivation of thiopurine drugs in the bone marrow. When TPMT activity is low, it is predicted that proportionately more 6-mercaptopurine can be converted into the cytotoxic 6-thioguanine nucleotides that accumulate in the bone marrow causing excessive toxicity. This test can also detect TMPT hyperactivity. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs, and therefore they cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity. The activity of TPMT is measured by 3 different substrates. Reports include the quantitative activity level of TPMT for each of 3 different substrates and an interpretation of these results. When abnormal results are detected, a detailed interpretation is given, including an overview of results and suggestion as to whether patient has TPMT deficiency or hyperactivity, as well as discussion of treatment considerations. TPMT phenotype testing does not replace the need for clinical monitoring of patients treated with thiopurine drugs. Genotype for TPMT cannot be inferred from TPMT activity (phenotype). Phenotype testing should not be requested for patients currently treated with thiopurine drugs. TPMT activity is measured in RBCs. If a patient has had a recent blood transfusion, within 30 to 60 days of testing, the patient's true enzyme activity may not be accurately reflected.

**Reference Values:**

3.00-6.66 nmol/mL/hour 6-Methylmercaptopurine (normal)  
5.04-9.57 nmol/mL/hour 6-Methylmercaptopurine riboside (normal)  
2.70-5.84 nmol/mL/hour 6-Methylthioguanine riboside (normal)

**Clinical References:**  
**Thiosulfate, Urine**

**Reference Values:**
Reporting limit determined each analysis

Creatinine (mg/L)
- U.S. Population (10th - 90th percentiles, median)
  - All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
  - Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
  - Females: 273 - 2170 mg/L, median 994 (n=11,635)

Thiosulfate (mcg/mL)
- Generally less than 9.2 mcg/mL (based on a median creatinine concentration of 1.18 g/L)

Thiosulfate (Creatinine corrected) (mg/g Creat)
- Generally less than 7.8 mg/g creatinine

**Thiothixene (Navane)**

**Reference Values:**
Reference Range: 10.0 - 30.0 ng/mL

**Thrombin Time (Bovine), Plasma**

**Clinical Information:** Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of many of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time and activated partial thromboplastin time are first-order tests for coagulation abnormalities and are prolonged in many disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. Thrombin catalyzes the transformation of fibrinogen to fibrin (by cleaving fibrinopeptides A and B), which is followed by polymerization of fibrin to form a clot. The thrombin time (TT) test measures the time of clot formation when thrombin is added to citrated plasma. The phospholipid-dependent procoagulant enzyme cascades (intrinsic, extrinsic, and "common" pathway) are bypassed by the addition of exogenous thrombin. Therefore, the TT mainly reflects functions and interactions of solution-phase exogenous thrombin and endogenous fibrinogen.

**Useful For:** Detecting or excluding the presence of heparin or heparin-like anticoagulants (which act by enhancing antithrombin's inhibition of thrombin and other procoagulant enzymes) when used in conjunction with the reptilase time (RT) in evaluating unexplained prolonged clotting times Identifying the cause of a prolonged prothrombin time, activated partial thromboplastin time, or dilute Russell viper venom time when used in conjunction with the RT and fibrinogen assay

**Interpretation:** Prolongation of the thrombin time (TT) is consistent with the presence of heparin-like anticoagulants, hypofibrinogenemia, dysfibrinogenemia, fibrin degradation products, and antibody inhibitors of thrombin. An immeasurably prolonged TT is usually the result of heparin in the specimen or, rarely, the presence of thrombin antibodies or afibrinogenemia. When the TT test is performed with diluted bovine thrombin to achieve a normal plasma clotting time of about 20 seconds, the TT is capable of detecting unfractionated heparin at a concentration of 0.05 units/mL of heparin. Other tests useful in interpreting the significance of prolongation of the TT include: reptilase time (RT), human thrombin time, clottable fibrinogen assay, and the fibrin D-dimer assay. These tests are available as components of coagulation profile test panels. As seen in the following table, RT can help distinguish among the various causes of a prolonged TT. Thrombin time Reptilase time Causes Remarks Prolonged Prolonged Hypo- or
afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay

**Reference Values:**
15.8-24.9 seconds

**Clinical References:**
5. Turgeon TL, ed: Clinical Hematology. 6th ed. Wolkers Kluer and Co; 2018

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**Thrombin-Antithrombin Complex**

**Clinical Information:** Thrombin-antithrombin complexes (TAT) form covalently following thrombin generation and have a plasma half-life of 10 to 15 minutes. The presence of TAT indicates ongoing thrombin generation and the consumption of antithrombin. Upon activation of coagulation, antithrombin complexes with thrombin as well as other serine proteases. Complex formation is greatly enhanced by the presence of heparin or other glycosaminoglycans. The reaction initially is reversible, but becomes irreversible following the formation of a covalent bond between antithrombin and thrombin. This binding results in complete inhibition of thrombin's activity. Elevated levels of TAT may be associated with advancing age, pregnancy, septicemia, disseminated intravascular coagulation, multiple traumas, acute pancreatitis, acute and chronic leukemia, pre-â-clampsia, acute and chronic liver disease, and other predisposing causes of thrombosis. Increased levels are also reported during heparin and fibrinolytic therapy. TAT levels are markedly reduced in the first 24 hours after receiving oral anticoagulants. The TAT assay can detect the intravascular generation of thrombin and provides valuable information in the diagnosis of thrombotic events. Decreasing TAT levels can also indicate the resolution of a thrombotic event. A normal TAT level in the presence of an elevated D-dimer may indicate an old thrombus. Elevated TAT measurements may be accompanied by increased levels of prothrombin fragment 1+2, fibrinopeptide A, fibrin(ogen)degradation products, and D-dimer. D-dimer has greater sensitivity for detection of deep venous thrombosis.

**Reference Values:**
<4.3 ng/mL

Pre-analytical conditions such as a difficult draw may spuriously increase test results.

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**Thrombophilia Profile Interpretation**

**Clinical Information:** Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations that have been linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, stillbirth). The current thrombophilia does not predict for arterial thrombosis. Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (eg, prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity deep vein thrombosis; this risk is unrelated to thrombophilia. Inherited thrombophilias include: -Deficiency due to reduced plasma protein level or dysfunctional protein of: Â - Antithrombin Â - Protein C Â - Protein S -Dysfibrinogenemias (rare) -Activated protein C resistance due to the
factor V R506Q (Leiden) mutation - Prothrombin G20210A mutation

Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis. Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF and are of uncertain significance with respect to thrombosis risk. Acquired deficiencies of protein C and protein S are also found in patients with liver disease who are being treated with oral anticoagulants (eg, warfarin, Coumadin), since both of these proteins are dependent upon the action of vitamin K for normal function. Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the level of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma) and the portion of bound protein S also rises leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

**Useful For:** Evaluating patients with thrombosis or hypercoagulability states
Detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis
Detecting a deficiency of antithrombin, protein C, or protein S
Detecting activated protein C resistance (and the factor V R506Q [Leiden] mutation if indicated)
Detecting the prothrombin G20210A mutation

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Only orderable as part of a profile. For more information see AATHR / Thrombophilia Profile, Plasma.

An interpretive report will be provided.

**Clinical References:**
of protein C and protein S are also found in patients with liver disease who are being treated with oral anticoagulants (eg, warfarin, Coumadin), since both of these proteins are dependent upon the action of vitamin K for normal function. Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the level of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma) and the portion of bound protein S also rises leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

**Useful For:** Evaluating patients with thrombosis or hypercoagulability states Detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis Detecting a deficiency of antithrombin, protein C, or protein S Detecting activated protein C resistance (and the factor V R506Q [Leiden] variant if indicated) Detecting the prothrombin G20210A variant

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FFTPO**

**Thrombopoietin (TPO)**

**Reference Values:**
7 Aeâ€“â€œ 99 pg/mL

**THSIF**

**Thrombospondin Type 1 Domain Containing 7A (THSD7A), Immunofluorescence**

**Clinical Information:** Thrombospondin type 1 domain-containing 7A (THSD7A) is a target antigen in membranous nephropathy (MN) and is detected in approximately 3% to 5% of non-PLA2R-associated MN patients. Differentiating THSD7A-associated MN from PLA2R-associated MN is critical as approximately 20% of patients with THSD7A-associated MN have solid malignancy suggesting that THSD7A-associated MN is more likely to be secondary to malignancy than PLA2R-associated MN.

**Useful For:** Diagnosis of thrombospondin type 1 domain-containing 7A (THSD7A)-associated membranous nephropathy

**Interpretation:** Staining is interpreted and reported as negative or positive.

**Clinical References:**

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**THSD7**

**Thrombospondin Type-1 Domain-Containing 7A Antibodies,**

Current as of June 14, 2021 12:13 pm CDT

800-533-1710 or 507-266-5700 or mayocliniclabs.com
Serum

Clinical Information: Recently, autoantibodies against phospholipase A2 receptor (PLA2R) in the kidney were determined to be the major target antigen for patients with idiopathic/primary membranous nephropathy (MN).(1) Approximately 70% of patients with primary MN circulate anti-PLA2R antibodies, and in the remaining 30% (who are PLA2R-negative), antithrombospondin type-1 domain-containing 7A (THSD7A) was shown to have approximately a 10% prevalence (or about 3% of all primary MN patients).(2) Mouse podocytes express THSD7A and introduction of anti-THSD7A autoantibodies induces MN in murine models. Mouse podocytes do not express PLA2R so exogenous administration of anti-PLA2R does not recapitulate membranous nephropathy in mice.(3) Additionally, THSD7A has been described as a potential tumor antigen and, thus, it has been suggested that THSD7A-positive patients merit a thorough cancer screening.(4)

Useful For: Distinguishing primary from secondary membranous nephropathy

Interpretation: Therapy outcome can be monitored by measuring the antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

Reference Values:
Negative


Thyme, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to thyme Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Thyrogbolin Antibody, Serum**

**Clinical Information:** Thyroglobulin autoantibodies bind thyroglobulin (Tg), a major thyroid-specific protein. Tg plays a crucial role in thyroid hormone synthesis, storage, and release. Tg is not secreted into the systemic circulation under normal circumstances. However, follicular destruction through inflammation (thyroiditis and autoimmune hypothyroidism), hemorrhage (nodular goiter), or rapid disordered growth of thyroid tissue, as may be observed in Graves disease or follicular cell-derived thyroid neoplasms, can result in leakage of Tg into the blood stream. This results in the formation of autoantibodies to Tg (anti-Tg) in some individuals. The same processes also may result in exposure of other "hidden" thyroid antigens to the immune system, resulting in the formation of autoantibodies to other thyroid antigens, in particular thyroid peroxidase (TPO) (anti-TPO). Since anti-Tg and anti-TPO autoantibodies are observed most frequently in autoimmune thyroiditis (Hashimoto disease), they were originally considered to be of possible pathogenic significance in this disorder. However, the consensus opinion today is that they are merely disease markers. It is felt that the presence of competent immune cells at the site of thyroid tissue destruction in autoimmune thyroiditis simply predisposes the patient to form autoantibodies to hidden thyroid antigens. In individuals with autoimmune hypothyroidism, 30% to 50% will have detectable anti-Tg autoantibodies, while 50% to 90% will have detectable anti-TPO autoantibodies. In Graves disease, both types of autoantibodies are observed at approximately half these rates. The presence of anti-Tg, which occurs in 15% to 30% of thyroid cancer patients, could result in misleading Tg results. In immunometric assays, the presence of thyroid antibody can lead to false-low measurement; whereas it might lead to false-high results in competitive assays.

**Useful For:** As an adjunct in the diagnosis of autoimmune thyroid diseases: Hashimoto disease, postpartum thyroiditis, neonatal hypothyroidism, and Graves disease

**Interpretation:** Diagnosis of Autoimmune Thyroid Disease: Measurements of antithyroperoxidase (TPO) have higher sensitivity and equal specificity to antithyroglobulin (anti-Tg) measurements in the diagnosis of autoimmune thyroid disease. Anti-Tg levels should, therefore, only be measured if anti-TPO measurements are negative, but clinical suspicion of autoimmune thyroid disease is high.

Detection of significant titer of anti-Tg or anti-TPO autoantibodies is supportive evidence for a diagnosis of Graves disease in patients with thyrotoxicosis. However, measurement of the pathogenic antithyrotropin (anti-thyroid stimulating hormone)) receptor antibodies by binding assay (THYRO / Thyrotropin Receptor Antibody, Serum) or bioassay (TSI / Thyroid-Stimulating Immunoglobulin, Serum) is the preferred method of confirming Graves disease in atypical cases and under special clinical circumstances. Positive thyroid autoantibody levels in patients with high-normal or slightly elevated
serum thyrotropin levels predict the future development of more profound hypothyroidism. Patients with postpartum thyroiditis with persistently elevated thyroid autoantibody levels have an increased likelihood of permanent hypothyroidism. In cases of neonatal hypothyroidism, the detection of anti-TPO or anti-Tg in the infant suggests transplacental antibody transfer, particularly if the mother has a history of autoimmune thyroiditis or detectable thyroid autoantibodies. The neonatal hypothyroidism is likely to be transient in these cases.

**Reference Values:**

<4.0 IU/mL

Reference values apply to all ages.

**Clinical References:**


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**THYR 70565**

**Thyroglobulin Immunostain, Technical Component Only**

**Clinical Information:** Thyroglobulin is a glycoprotein product of thyroid epithelial cells, which is then complexed with iodine before being secreted as thyroid hormone in the blood. In normal thyroid, thyroglobulin staining is seen at the apical surface of thyrocytes and within the colloid in the center of thyroid follicles. The thyroglobulin antibody is useful in classifying poorly differentiated or metastatic thyroid carcinomas.

**Useful For:** Classification of thyroid carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


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**TGMS 62749**

**Thyroglobulin Mass Spectrometry, Serum**

**Clinical Information:** Thyroglobulin (Tg) is a highly thyroid-specific large homodimeric glycoprotein (approximately 660 KDa). It contains 8% to 10% of carbohydrates and iodine. Thyroxine (T4) and triiodothyronine (T3) are synthesized on Tg within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy...
individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is highly organ-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during primary treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of more than 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious. There are 3 situations, when serum Tg measurement might be misleading: 1. Remnant thyroid tissue (see above, 0.5-1 ng/mL Tg per gram) 2. Antithyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, can lead to false-low measurement in immunometric assays (most commonly used); in competitive assays they may cause false-high results. 3. Heterophile antibodies (HAb) are antibodies that are capable of interacting with the antibodies used in immunoassays, usually resulting in false-high measurements. Depending on the assay and the patient population, this can lead to erroneously high results in 0.1% to 3.0% of patients. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb or HAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

**Useful For:** Accurate measurement of serum thyroglobulin (Tg) in patients with known or suspected antithyroglobulin autoantibodies (TgAb) or heterophile antibodies (HAb) Reflex testing of samples with previously unknown TgAb status that prove TgAb positive during immunoassay testing Assisting in the differential diagnosis of early phase silent thyroiditis versus Graves' disease in patients without thyroid cancer (the mass spectrometry-based method would only be required if these patients have TgAb or HAb)

**Interpretation:** Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay limit of quantification below 1 ng/mL; for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum antithyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb (< or =20 kIU/L). If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results. If the apparent Tg concentration is below 1 ng/mL, the sample should be remeasured by mass spectrometry. This will allow confident detection of Tg in the presence of TgAb down to 0.2 ng/mL (risk of residual/recurrent disease <1-3%). Samples from patients with Tg concentrations above 1 ng/mL (or 2 ng/mL; there is some discussion in the literature) might not require Tg measurement by mass spectrometry, because current guidelines suggest further work-up might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest at best when Tg is just above this threshold (3%-25%, rising in parallel with Tg concentrations up to 10 ng/mL) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, it might therefore also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is above 1.0 ng/mL, but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations between 1.0 and 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. There are no routine tests that can detect heterophile antibodies in patient samples. An unexpected high result is usually the tip-off in this case and should prompt remeasurement by mass spectrometry, which will provide a reliable result. It has been determined that the presence of TgAb in serum can lead to underestimation of Tg concentration by immunoassay methods. When antibodies are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, 20% of specimens...
containing antibodies that are negative for Tg by immunoassay tested positive by liquid chromatography-tandem mass spectrometry (LC-MS/MS); no results over 3 ng/mL by LC-MS/MS were observed. In rare cases, when Tg is measured in patients with an intact thyroid gland who do not have thyroid cancer, substantial elevations will primarily be observed in very large goiters, highly active Graves disease, and, most pronounced, in the early phase of acute thyroiditis when follicular destruction releases massive amounts of stored Tg into the circulation. Levels are often well above 100 ng/mL.

**Reference Values:**

Healthy individuals with intact, functioning thyroid: < or =33 ng/mL

The reference ranges listed below, however, are for thyroid cancer follow up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin (Tg) measurements. Ranges are based on best practice guidelines and the literature, which includes Mayo Clinic studies, and represent clinical decision levels.

Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.2-1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level.

- Tg <0.2 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements, and radiiodine ablation status. Undetectable Tg levels in athyrotic individuals on suppression therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer.

- Tg > or =0.2 ng/mL to 2.0 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements, and radiiodine ablation status. Tg levels of 0.2-2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer.

- Tg 2.1 ng/mL to 9.9 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radiiodine ablation status. Tg levels of 2.1-9.9 ng/mL in athyrotic individuals on suppression therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer.

- Tg > or =10 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radiiodine ablation status. Tg levels of 10 ng/mL or above in athyrotic individuals on suppressive therapy indicate a significant (>25%) risk of clinically detectable recurrent papillary/follicular thyroid cancer.

**Clinical References:**


**Clinical Information:** Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 KDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen.
of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis) larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of more than 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious. The presence of anti-thyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to false low measurement; whereas it might lead to false high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

**Useful For:** Reporting of accurate thyroglobulin results, depending on the antithyroglobulin antibodies status of the patient Accurate measurement of serum thyroglobulin in patients with known or suspected antithyroglobulin autoantibodies or possible heterophile antibodies

**Interpretation:** Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay - limit of quantification less than 1 ng/mL; for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum anti-thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results. If the apparent Tg concentration is less than 1.0 ng/mL, the sample should be remeasured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). This will allow confident detection of Tg in the presence of TgAb down to 0.5 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations greater than 1.0 ng/mL might not require Tg measurement by mass spectrometry, because current guidelines suggest further work-up might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to greater than 90% risks. In selected patients, it might therefore also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is greater than 1.0 ng/mL, but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of anti-thyroglobulin autoantibodies (TgAb) in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, some specimens containing TgAb which are negative for Tg by immunoassay tested positive by LC-MS/MS. Therefore, measuring of Tg by LC-MS/MS is the preferred method in TgAb positive patients. The listed decision levels are for thyroid cancer follow-up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Decision levels are based on best practice guidelines and the literature, which includes Mayo Clinic studies. Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.2 to 1.0 ng/mL per gram of remnant tissue, depending on the TSH level.
Thyroglobulin by Mass Spectrometry: Tg <0.2 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Undetectable Tg levels in athyrotic individuals on suppression therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.2 ng/mL to 2.0 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Tg levels of 0.2-2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg 2.1 ng/mL to 9.9 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of 2.1-9.9 ng/mL in athyrotic individuals on suppression therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant (>25%) risk of clinically detectable recurrent papillary/follicular thyroid cancer. Thyroglobulin by Immunoassay: Tg <0.1 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels <0.1 ng/mL in athyrotic individuals on suppressive therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.1 to 2.0 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 0.1 to 2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg 2.1 ng/mL to 9.9 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 2.1 to 9.9 ng/mL in athyrotic individuals on suppressive therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant risk (>25%) of clinically detectable recurrent papillary/follicular thyroid cancer.

Reference Values:
Thyroglobulin Antibody: <1.8 IU/mL


Thyroglobulin, Tumor Marker, Fine-Needle Aspiration Biopsy Needle Wash

Clinical Information: Thyroglobulin (Tg) is a 660,000 Da glycoprotein produced exclusively by the follicular cells of the thyroid. Given the tissue specificity of Tg production, measurement of serum concentrations in athyrotic patients enables detection of persistence, recurrence, or metastasis of differentiated thyroid carcinoma. In addition, Tg measurement in biopsy specimens of nonthyroidal tissues may assist in confirming and localizing metastatic disease. In papillary thyroid carcinoma (PTC), which accounts for greater than 80% of all thyroid cancer cases, most metastatic disease occurs in loco-regional lymph nodes in the neck, which are easily examined by ultrasound. Most suspicious nodes undergo ultrasonography-guided fine-needle aspiration biopsy (FNAB) for cytology examination to determine a diagnosis. Unfortunately, in up to 20% of cases, inadequate cellularity or nonrepresentative sampling precludes the diagnosis. Measurement of Tg in FNAB washes from lymph nodes suspected of metastatic PTC is used as an adjunct to cytology examination after ultrasound-guided FNAB in situations where cytology is inconclusive. One of the advantages of the measurement of Tg in FNAB washes is that a dedicated needle pass is not necessary for analysis. Most often, the washout is performed by rinsing the FNAB needle with a small volume of saline immediately after the cellular component of the biopsy has
been expelled for cytological examination. The diagnostic performance of Tg in FNAB washouts often allows for the accurate diagnosis of cases in which cytology is non-diagnostic. A meta-analysis that included 24 studies and 2865 lymph nodes reported a pooled sensitivity of 95% and specificity of 94% for detection of metastatic PTC. The diagnostic performance of Tg in FNAB washes is superior in athyrotic patients. In studies that included patients with the thyroid gland, the sensitivity was 86.2% and specificity was 90.2%. Including only patients after thyroidectomy showed improved performance with a sensitivity of 96.9% and specificity of 94.1%. In an in-house study, a Tg cut-off of 1 ng/mL for FNAB-needle wash specimens provided 100% sensitivity and 96.2% specificity for the detection of metastatic thyroid carcinoma in lymph nodes from athyrotic patients. The diagnostic performance of Tg at the 1-ng/mL cut-off compared favorably with cytology (95.1% overall agreement) and allowed accurate diagnosis in 18 of the 19 cases in which cytology was nondiagnostic or not performed. A number of professional guidelines recommend the measurement of Tg in FNAB washouts from lymph nodes in cases of inadequate cytology or cases with conflicting cytological and ultrasound evaluations. Interpretation of Tg concentrations in FNAB needle washes from tissues other than lymph nodes is not well defined and needs to be considered in the case by case basis. The most established use is to determine the tissue origin of a thyroid mass/nodule or other neck mass/nodule that is suspected to be thyroid derived. This can be accomplished by measuring Tg, calcitonin and parathyroid hormone in the lesion. Measurement of Tg in thyroid bed tissue in patients, who underwent total thyroidectomy and radioactive iodine ablation, is a relatively frequent application of Tg testing, and may differentiate scar tissue from residual normal thyroid tissue. Finally, occasionally lesions in other organs might be biopsied to determine by Tg measurement if they are thyroid derived, if cytology/histology in not informative.

**Useful For:** Confirming or excluding metastases in enlarged or ultrasonographically suspicious lymph nodes from athyrotic individuals treated for differentiated thyroid cancer in conjunction with cytologic analysis Confirming or excluding the presence of thyroid tissue in the biopsied area from athyrotic individuals treated for differentiated thyroid cancer in conjunction with cytologic analysis This test is not useful for screening asymptomatic individuals for neoplastic disease.

**Interpretation:** Lymph Nodes: In athyrotic patients with a history of differentiated thyroid carcinoma, thyroglobulin (Tg) concentration greater than 1.0 ng/mL in the fine-needle aspiration biopsy (FNAB) needle wash suggests the presence of metastatic differentiated follicular cell-derived thyroid carcinoma in the biopsied area. Tg measurements yield reliable results in most cases with nondiagnostic cytology and are approximately equal in diagnostic accuracy to cytological examinations that are deemed sufficient for diagnosis. Non-lymph nodes: When measuring Tg in FNAB needle washes from thyroid bed tissue after total thyroidectomy and radioactive iodine ablation to differentiate thyroid versus scar tissue, an undetectable Tg concentration will be consistent with the absence of thyroid-derived tissue (including thyroid carcinoma) at the site biopsied. Detectable Tg concentration is consistent of the presence of thyroid-derived tissue, but it is not indicative of the presence of malignancy. Measurement of Tg in FNAB needle washes from a thyroid nodule may be used to distinguish parathyroid versus follicular cell derived and C-cell derived thyroid tissue but cannot identify a malignant process in the nodule. For all other biopsied sites, eg, lung, kidney, liver, brain, bone, and various other sites, absence of measurable Tg in FNAB needle washes is consistent with the absence of thyroid-derived tissue (including thyroid carcinoma) at the site biopsied. A detectable Tg concentration is consistent of the presence of thyroid-derived tissue, but it is not necessarily indicative of the presence of malignancy.

**Reference Values:**
- Lymph node: < or =1.0 ng/mL
  - This cutoff has been validated for total needle wash volumes of < or =1.5 mL of normal saline. If wash volumes are substantially larger, a lower cutoff might apply.
  - Non Lymph node: an interpretation will be provided

Thyroglobulin, Tumor Marker, Serum

Clinical Information: Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 KDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone: TSH level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis) larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is treated during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of more than 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious. The presence of antithyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to false-low results; whereas it might lead to false-high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg by mass spectrometry. Refer to TGMS / Thyroglobulin Mass Spectrometry, Serum for accurate sample analysis of patients who are known to be TgAb positive. If TgAb status is unknown, refer to HTGR / Thyroglobulin, Tumor Marker Reflex to LC-MS/MS or Immunoassay. When HTGR is ordered, TgAb testing is performed first. If TgAb is negative (<1.8 IU/mL), Tg is assayed by immunoassay (sensitive down to 0.1 ng/mL). If TgAb is positive, Tg is assayed by mass spectrometry (sensitive down to 0.2 ng/mL).

Useful For: Follow-up of patients with differentiated thyroid cancers after thyroidectomy and radioactive iodine ablation

Interpretation: Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay (limit of quantification <1.0 ng/mL); for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results if using an immunometric assay. If the apparent Tg concentration is <1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow accurate detection of Tg, in the presence of TgAb, down to 0.2 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations >1.0 ng/mL might not require Tg measurement by mass spectrometry, because current guidelines suggest further workup might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, therefore, it might also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is >1.0 ng/mL, but not above the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of antithyroglobulin autoantibodies (TgAb) in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg...
values may be underestimated by up to 60% in immunoassays. In addition, approximately 20% of specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Therefore, measuring of Tg by mass spectrometry is the preferred method in TgAb positive patients. The decision levels listed below, are for thyroid cancer follow up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Decision levels are based on best practice guidelines and the literature, which includes Mayo Clinic studies. Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.5 to 1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level. Tg <0.1 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radiiodine ablation status. Tg levels <0.1 ng/mL in athyrotic individuals on suppressive therapy indicate a minimal risk (<1-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.1 to 2.0 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radiiodine ablation status. Tg levels 0.1 to 2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg 2.1 to 9.9 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radiiodine ablation status. Tg levels 2.1 to 9.9 ng/mL in athyrotic individuals on suppressive therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radiiodine ablation status. Tg levels > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant risk (>25%) of clinically detectable recurrent papillary/follicular thyroid cancer.

Reference Values:

THYROGLOBULIN, TUMOR MARKER
Athyrotic: <0.1 ng/mL
Intact thyroid < or =33 ng/mL

THYROGLOBULIN ANTIBODY
<1.8 IU/mL
Reference values apply to all ages.

Clinical References:

Thyroid Autoantibodies Profile, Serum

Clinical Information: See individual unit codes.
Useful For: See individual unit codes.
Interpretation: See individual unit codes.

Reference Values:

THYROGLOBULIN ANTIBODY
<4.0 IU/mL
Reference values apply to all ages.

THYROPEROXIDASE ANTIBODIES
THSCM
Thyroid Function Cascade, Serum

Clinical Information: This test utilizes a cascaded testing procedure to efficiently evaluate and monitor functional thyroid status. The cascade begins with thyroid-stimulating hormone (TSH) as a screening assay. In patients with an intact pituitary-thyroid axis, TSH provides a physiologic indicator of the functional level of thyroid hormone activity. Increased TSH indicates inadequate thyroid hormone, and suppressed TSH indicates excess thyroid hormone. Transient TSH abnormalities may be found in seriously ill, hospitalized patients, so this is not the ideal setting to assess thyroid function. However, even in these patients, TSH works better than total thyroxine (an alternative screening test). When TSH is normal, no additional testing will be necessary. However, when the TSH result is abnormal, appropriate follow-up tests will automatically be performed. If TSH is below 0.3 mIU/L or above 4.2 mIU/L, free thyroxine (FT4) is performed. The supplemental measurement of FT4 in patients with abnormal TSH measurements allows one to better assess the severity of the changes. Serum triiodothyronine (T3) levels often are depressed in sick and hospitalized patients, caused in part by the biochemical shift to the production of reverse T3. Therefore, T3 generally is not a reliable predictor of hypothyroidism. However, in a small subset of hyperthyroid patients, hyperthyroidism may be caused by overproduction of T3 (T3 toxicosis). To help diagnose and monitor this subgroup, T3 is measured on all specimens with suppressed TSH and normal FT4 concentrations. Detectable concentrations of antithyroperoxidase (anti-TPO) antibodies are observed in patients with autoimmune thyroiditis and may cause the destruction of thyroid tissue, eventually resulting in hypothyroidism. Anti-TPO antibodies are measured in all specimens with elevated TSH concentrations. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Screening for a diagnosis of thyroid disease

Interpretation: In primary hypothyroidism, thyroid-stimulating hormone (TSH) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation test with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

Reference Values:
0-5 days: 0.7-15.2 mIU/L
6 days-2 months: 0.7-11.0 mIU/L
3-11 months: 0.7-8.4 mIU/L
1-5 years: 0.7-6.0 mIU/L
6-10 years: 0.6-4.8 mIU/L
11-19 years: 0.5-4.3 mIU/L
> or =20 years: 0.3-4.2 mIU/L

Thyroid Transcription Factor (8G7G3/1) Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Given its relative specificity for cells of thyroid or lung origin, this immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

Useful For: Identification of thyroid or lung cells as the primary tumor site in carcinomas of unknown origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Thyroid Transcription Factor (SPT24) Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Given its relative specificity for cells of thyroid or lung origin, this immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

Useful For: Part of a panel of immunostains to identify the primary site for carcinomas of unknown origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Thyroid Transcription Factor 1 (TTF1) (SPT24) and Keratin 5 (KRT5) Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein (detected by the chromogen 3,3'-diaminobenzidine: DAB) expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Keratin 5 is a type II cytokeratin (detected by the chromogen fast red) that dimerizes with the type I cytokeratin 14 forming intermediate filaments in the basal layer of the epidermis. Keratin 5 is useful for differentiating squamous cell carcinoma (KRT5 positive) from pulmonary adenocarcinomas (KRT5 negative). This immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

Useful For: Thyroid transcription factor 1 aids in the classification of carcinomas of unknown origin. Keratin 5 aids in the identification of squamous cell carcinoma.

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Thyroid-Stimulating Hormone (TSH), Beta Immunostain, Technical Component Only

Clinical Information: Thyroid-stimulating hormone (TSH) stimulates thyroid growth and production of thyroid hormones. TSH-producing cells constitute approximately 5% of the cells of the normal anterior pituitary. Antibodies to TSH are used in a panel to subclassify pituitary adenomas.

Useful For: Part of a panel of immunostains used in the classification of pituitary adenomas.
**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**STSH**

**Thyroid-Stimulating Hormone-Sensitive (s-TSH), Serum**

**Clinical Information:** Thyrotropin (TSH, thyroid-stimulating hormone) is a glycoprotein hormone consisting of 2 subunits. The alpha subunit is similar to those of follicle-stimulating hormone, human chorionic gonadotropin, and luteinizing hormone. The beta subunit is different from those of the other glycoprotein hormones and confers its biochemical specificity. TSH is synthesized and secreted by the anterior pituitary in response to a negative feedback mechanism involving concentrations of free triiodothyronine and free thyroxine. Additionally, the hypothalamic tripeptide, thyrotropin-releasing hormone, directly stimulates TSH production. TSH interacts with specific cell receptors on the thyroid cell surface and gives rise to 2 main actions. First, it stimulates cell reproduction and hypertrophy. Second, it stimulates the thyroid gland to synthesize and secrete triiodothyronine and thyroxine. Serum TSH concentrations exhibit a diurnal variation with the peak occurring during the night and the nadir occurring between 10 a.m. and 4 p.m. This biological variation does not influence the interpretation of the test result since most clinical TSH measurements are performed on ambulatory patients between 8 a.m. and 6 p.m. When hypothalamic-pituitary function is normal, a log/linear inverse relationship between serum TSH and free thyroxine exists. See Thyroid Function Ordering Algorithm in Special Instructions.

**Useful For:** Screening for thyroid dysfunction and detecting mild (subclinical), as well as overt, primary hypo- or hyperthyroidism in ambulatory patients Monitoring patients on thyroid replacement therapy Confirmation of thyrotropin (TSH, thyroid-stimulating hormone) suppression in thyroid cancer patients on thyroxine suppression therapy Prediction of thyrotropin-releasing hormone-stimulated TSH response

**Interpretation:** In primary hypothyroidism, thyrotropin (TSH, thyroid-stimulating hormone) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

**Reference Values:**
- 0-5 days: 0.7-15.2 mIU/L
- 6 days-2 months: 0.7-11.0 mIU/L
- 3-11 months: 0.7-8.4 mIU/L
1-5 years: 0.7-6.0 mIU/L
6-10 years: 0.6-4.8 mIU/L
11-19 years: 0.5-4.3 mIU/L
> or =20 years: 0.3-4.2 mIU/L

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

**Clinical References:**

**Thyroid-Stimulating Immunoglobulin, Serum**

**Clinical Information:** Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin receptor (thyroid-stimulating hormone receptor: TSHR), thyroid-peroxidase (TPO), and thyroglobulin (Tg), as well as an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. The role of the TPO and Tg autoantibodies in either autoimmune thyrotoxicosis or autoimmune hypothyroidism is less well established; they may merely represent epiphenomena. Detectable concentrations of anti-TPO antibodies are observed in most patients with autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease). Autoantibodies that bind and transactivate the TSHR lead to stimulation of the thyroid gland independent of the normal feedback-regulated thyroid-stimulating hormone (TSH) stimulation. These TSHR autoantibodies also are known as long-acting-thyroid-stimulator or thyroid-stimulating immunoglobulins (TSI). Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. At least 20% of patients with autoimmune hypothyroidism also have evidence either of TSHR-blocking antibodies or, less commonly, TSI. TSHR autoantibodies may be found before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease are aimed at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent cure. TSI are IgG antibodies and can, therefore, cross the placental barrier, causing neonatal thyrotoxicosis. First-order tests for autoimmune thyroid disease include TPO / Thyroperoxidase (TPO) Antibodies, Serum (most suited for suspected cases of autoimmune hypothyroidism) and THYRO / Thyrotropin Receptor Antibody, Serum. Thyrotropin receptor antibody (TSHR-antibody) is a binding assay that detects both TSI and TSHR-blocking autoantibodies; it can be used instead of this TSI assay for most applications, as long as the results are interpreted in the clinical context. The TSHR-antibody test has a shorter turnaround time than the TSI assay, is less expensive, and if interpreted within the clinical context, has excellent correlation with the TSI assay. Specific detection of TSI is accomplished by this second-order bioassay.

**Useful For:** Second-order testing for autoimmune thyroid disease, including:
- Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical signs or contraindicated (eg, pregnant or breast-feeding) or indeterminate thyroid radioisotope scans
- Diagnosis of clinically suspected Graves disease (eg, extrathyroidal manifestations of Graves disease: endocrine exophthalmos, pretibial myxedema, thyroid acropathy) but normal thyroid function tests
- Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past Graves disease
- Differential diagnosis of gestational thyrotoxicosis versus first-trimester manifestation or recurrence of Graves disease
- Assessing the risk of Graves disease relapse after antithyroid drug treatment A combination of TSI /
Thyroid-Stimulating Immunoglobulin (TSI), Serum and THYRO / Thyrotropin Receptor Antibody, Serum is useful as an adjunct in the diagnosis of unusual cases of hypothyroidism (eg, Hashitoxicosis).

**Interpretation:** The sensitivity and specificity of an elevated thyroid-stimulating immunoglobulins (TSI) index for Graves disease diagnosis depends on whether patients have clinically active, untreated disease or disease treated with antithyroid drugs. Using a TSI index of 1.3 as the cutoff level in newly diagnosed, untreated patients, the sensitivity and specificity are higher than 90%. For a higher cutoff of 1.8, specificity approaches 100%, but sensitivity decreases somewhat. In patients with inactive or treated Graves disease the specificity is similar, while sensitivity is lower, ranging from 50% to 80%. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has a TSI index above 3.9 during the last trimester, regardless of her remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. This is particularly relevant for women who have previously undergone thyroid-ablative therapy or are on active antithyroid drug treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyroid-stimulating hormone receptor (TSHR) and transient changes in thyroid hormone protein binding, is not associated with an elevated TSI index. Finding an elevated TSI index in this setting suggests underlying Graves disease. An elevated TSI index at the conclusion of a course of anti-thyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TSI index, is not predictive of prolonged remission. In patients with thyroid function tests that fluctuate between hypo- and hyperthyroidism or vice versa, a clearly elevated TSHR-antibody level (>25%) and a simultaneous TSI index that is normal or only minimally elevated (1.3-1.8) suggest a diagnosis of possible Hashitoxicosis.

**Reference Values:**
- < or =1.3 TSI index
- Reference values apply to all ages.

**Clinical References:**

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**Thyroperoxidase Antibodies, Serum**

**Clinical Information:** Thyroperoxidase (TPO) is an enzyme involved in thyroid hormone synthesis, catalyzing the oxidation of iodide on tyrosine residues in thyroglobulin for the synthesis of triiodothyronine and thyroxine (tetraiodothyronine). TPO is a membrane-associated hemoglycoprotein expressed only in thyrocytes and is one of the most important thyroid gland antigens. Disorders of the thyroid gland are frequently caused by autoimmune mechanisms with the production of autoantibodies. Anti-TPO antibodies activate complement and are thought to be significantly involved in thyroid dysfunction and the pathogenesis of hypothyroidism. The determination of TPO antibody levels is the most sensitive test for detecting autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease) and detectable concentrations of anti-TPO antibodies are observed in most patients with these disorders. The highest TPO antibody levels are observed in patients suffering from Hashimoto thyroiditis. In this disease, the prevalence of TPO antibodies is about 90% of cases, confirming the autoimmune origin of the disease. These autoantibodies also frequently occur (60%-80%) in the course of Graves disease. In patients with subclinical hypothyroidism, the presence of TPO antibodies is associated with an increased risk of developing overt hypothyroidism. Many clinical endocrinologists use the TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism, and Mayo Clinic Laboratories endorses this practice. See Thyroid Function Ordering Algorithm in Special Instructions.

**Useful For:** Aiding in the diagnosis of thyroid autoimmune disorders Differentiating thyroid autoimmune disorders from nonautoimmune goiter or hypothyroidism As a diagnostic tool in deciding
whether to treat a patient who has subclinical hypothyroidism

**Interpretation:** Values above 9.0 IU/mL generally are associated with autoimmune thyroiditis, but elevations are also seen in other autoimmune diseases. In patients with subclinical hypothyroidism, the presence of thyroperoxidase (TPO) antibodies predicts a higher risk of developing overt hypothyroidism, 4.3% per year versus 2.1% per year in antibody-negative individuals. Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases, such as adrenal insufficiency and type 1 diabetes. The frequency of detectable anti-TPO observed in nonimmune thyroid disease is similar to the 10% to 12% observed in a healthy population with normal thyroid function. There is a good association between the presence of autoantibodies against TPO and histological thyroiditis. However, in view of the extensive regenerative capacity of the thyroid under the influence of thyroid-stimulating hormone, chronic thyroid disease may be present for years before the clinical manifestation of hypothyroidism becomes evident, if ever.

**Reference Values:**

<9.0 IU/mL

Reference values apply to all ages.

**Clinical References:**

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**THYRO 81797**

**Thyrotropin Receptor Antibody, Serum**

**Clinical Information:** Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin receptor, thyroid peroxidase, and thyroglobulin, as well as by an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, thyrotropin receptor autoantibodies (TRAb) are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease; GD, Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of stimulating TRAb-. These autoantibodies, also known as long-acting-thyroid-stimulator (LATS) or thyroid-stimulating immunoglobulins (TSI), bind to the receptor and transactivate it, leading to stimulation of the thyroid gland independent of the normal feedback-regulated thyrotropin (TSH) stimulation. Some patients with GD also have TRAb, which do not transactivate the thyrotropin receptor. The balance between stimulating and blocking antibodies, as well as their individual titers, is felt to be a determinant of GD severity. Some patients with autoimmune hypothyroidism also have evidence of either blocking TRAb or, rarely, TSI. TRAb may be detected before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for GD are aimed at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent clinical cure. This is of particular relevance for pregnant women with a history of GD that was treated with thyroid-ablative therapy. Some of these women may continue to produce TSI. Since TSI are IgG antibodies, they can cross the placental barrier causing neonatal thyrotoxicosis. While the gold standard for thyroid-stimulating immunoglobulins is the bioassay (see TSI / Thyroid-Stimulating Immunoglobulin [TSI], Serum), the TRAb test has a shorter turnaround time, less analytical variability, and is less expensive.

**Useful For:** Recommended first-line test for detection of thyrotropin receptor antibodies The following situations: - Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical findings and/or contraindicated (eg, pregnant or breast-feeding) or nondiagnostic thyroid radioisotope scans - Diagnosis of clinically suspected Graves disease (GD) (eg, extrathyroidal manifestation of GD include endocrine exophthalmos, pretibial myxedema, thyroid acropathy) in patients with normal thyroid function tests - Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past active GD - Differential diagnosis of gestational thyrotoxicosis versus first trimester manifestation or recurrence of Gravesâ€™ disease - Assessing the risk of GD relapse after...
antithyroid drug treatment

**Interpretation:** The sensitivity and specificity of an elevated thyrotropin receptor antibody (TRAb) test for Graves disease (GD) diagnosis depends on whether patients have disease treated with antithyroid drugs or clinically active, untreated disease. Based on a study that included specimens from 436 apparently healthy individuals, 210 patients with thyroid diseases without diagnosis of GD, and 102 patients with untreated GD, a decision limit of 1.75 IU/L showed a sensitivity of 97% and a specificity of 99% for detection of GD. In healthy individuals and in patients with thyroid disease without diagnosis of GD, the upper limit of antithyrotropin receptor values are 1.22 IU/L and 1.58 IU/L, respectively (97.5th percentiles). A Mayo study of 115 patients, including 42 patients with GD, showed a sensitivity of 95% and a specificity of 97% for detection of GD at a decision limit of 1.75 IU/L. Assessment of TRAb status is particularly relevant in women who have undergone thyroid ablative therapy or are on active antithyroid treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of GD has TRAb concentrations of more than 3.25 IU/L during the last trimester, regardless of her clinical remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyrotropin receptor and transient changes in thyroid hormone protein binding, is only very rarely associated with an elevated TRAb test. Finding an elevated test result in this setting usually suggests underlying GD. An elevated TRAb test at the conclusion of a course of antithyroid drug treatment is highly predictive of relapse of GD. However, the converse, a normal TRAb test, is not predictive of prolonged remission.

**Reference Values:**

< or =1.75 IU/L


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**Thyroxine-Binding Globulin (TBG), Serum**

**Clinical Information:** Thyroxine binding globulin (TBG) is the high-affinity serum binding protein for thyroxine and triiodothyronine. Normally, the thyroid adjusts to changing concentrations of TBG by producing more, or less, thyroid hormone to maintain a constant level of metabolically important free hormone. Elevated TBG levels are associated with influences such as pregnancy, genetic predisposition, oral contraceptives, and estrogen therapy. TBG levels can decrease with androgenic or anabolic steroids, large doses of glucocorticoids, hypoproteinemic states, liver disease, nephrotic syndrome, and congenital TBG variants.

**Useful For:** Cases in which total thyroid hormone levels do not correlate with the thyrometabolic status, most commonly with pregnancy or the use of contraceptive steroids

**Interpretation:** A change in thyroxine-binding globulin (TBG) concentration may be of hereditary, pathophysiologic, or pharmacologic origin. The TBG concentration indicates whether an abnormally high or low total thyroid hormone concentration is offset by a parallel increase or decrease in TBG concentration. In TBG deficiency, one may find euthyroid patients with extremely low total thyroxine (T4) values. Conversely, patients with high TBG levels may be clinically euthyroid with high serum total T4 values. Twenty-four specimens obtained during various stages of pregnancy yielded results ranging from 27 to 66 mcg/mL with a median of 43 mcg/mL. The literature suggests 47 to 59 mcg/mL as the range of TBG values expected during the third trimester of pregnancy.

**Reference Values:**
Males: 12-26 mcg/mL
Females: 11-27 mcg/mL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html


**T4BPE 38507**

**Thyroxine-Binding Protein Electrophoresis, Serum**

Clinical Information: Normally, almost all thyroxine (99.5%) is bound to thyroxine-binding globulin, prealbumin, and albumin. Deficiencies and aberrant forms of these binding proteins can occur, causing difficulties interpreting thyroid function test results. Such abnormalities may be identified by thyroxine-binding protein electrophoresis.

Useful For: Explaining unusual thyroxine (T4), free T4, and thyroxine-binding globulin (TBG) test results that do not correlate with the patient’s clinical presentation Detecting the presence of aberrant thyroxine-binding proteins such as abnormal forms of albumin and prealbumin Detecting selective deficiency of one of the thyroxine-binding proteins Detecting antibodies to T4 An adjunct to the diagnosis of patients with high T4 concentration due to peripheral hormone resistance by ruling out thyroxine-binding abnormalities

Interpretation: An interpretive comment will be provided based on the total thyroxine concentration and the thyroxine binding protein profile observed in the electrophoresis.

**Reference Values:**

THYROXINE-BINDING PROTEIN ELECTROPHORESIS
10.3-24.9 mcg T4/dL bound to TBG
11.5-34.1 mcg T4/dL bound to albumin
48.8-70.4 mcg T4/dL bound to prealbumin

T4 (THYROXINE), TOTAL ONLY
Adult (> or ≥20 years): 4.5-11.7 mcg/dL
Pediatric:
0-5 days: 5.0-18.5 mcg/dL
6 days-2 months: 5.4-17.0 mcg/dL
3-11 months: 5.7-16.0 mcg/dL
1-5 years: 6.0-14.7 mcg/dL
6-10 years: 6.0-13.8 mcg/dL
11-19 years: 5.9-13.2 mcg/dL


**FGTIA 75019**

**Tiagabine (Gabitril), Serum**

Reference Values:

Report Limit: 5.0 ng/mL
Reference Range: <235.0 ng/mL

Therapeutic and toxic ranges have not been established.
Peak concentrations are expected at 45 minutes post dose; steady state is generally attained within 2 days.

Observed tiagabine concentrations in clinical trials (30 Å€â‚¬â€œ 56 mg/day): <1 Å€â‚¬â€œ 234 ng/mL

Measured tiagabine concentrations, post marketing (95% confidence interval): 0 Å€â‚¬â€œ 440 ng/mL

Note: The 95% confidence interval for tiagabine concentrations determined by MEDTOX Laboratories will be updated periodically as more information becomes available.

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**TICKS**

### Tick-Borne Disease Antibodies Panel, Serum

**Clinical Information:** In North America, ticks are the primary vectors of infectious diseases.(1) Worldwide, ticks rank second only to mosquitoes in disease transmission. In the United States, tickborne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic and granulocytic ehrlichiosis, babesiosis, tularemia, relapsing fever, and Colorado tick fever. Symptoms of the various tick-vectored diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A tickborne panel can assist in identifying the pathogen, allowing treatment to be initiated. For information on the specific diseases, see the individual test IDs.

**Useful For:** Evaluation of the most common tick-borne diseases found in the United States, including Lyme disease, human monocytic and granulocytic ehrlichiosis, and babesiosis Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms Seroepidemiological surveys of the prevalence of the infection in certain populations

**Interpretation:**

- **Ehrlichia chaffeensis:** A positive immunofluorescence assay (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection. Anaplasma phagocytophilum: A positive immunofluorescence assay (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection. During the acute phase of the infection, serologic tests are often nonreactive, polymerase chain reaction (PCR) testing is available to aid in the diagnosis of these cases (see EHRL / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood). Babesia microti: A positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2560. Lyme Disease: Negative: No evidence of antibodies to Borrelia burgdorferi detected. False-negative results may occur in recently infected patients (< or =2 weeks) due to low or undetectable antibody levels to B burgdorferi. If recent exposure is suspected, a second sample should be collected and tested in 2 to 4 weeks. Equivocal: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex. Positive: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex.

**Reference Values:**

- **Ehrlichia chaffeensis (HME) ANTIBODY, IgG**
  - <1:64
  - Reference values apply to all ages.

- **Anaplasma phagocytophilum ANTIBODY, IgG**
  - <1:64
Reference values apply to all ages.

Babesia microti IgG ANTIBODIES
<1:64
Reference values apply to all ages.

LYME DISEASE SEROLOGY
Negative
Reference values apply to all ages.


TKPNL
40203

Tick-Borne Panel, Molecular Detection, PCR, Blood

Clinical Information: Ticks are the primary vectors of infectious diseases in North America, and rank second only to mosquitoes in disease transmission worldwide. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic ehrlichiosis, human granulocytic anaplasmosis, babesiosis, tularemia, relapsing fever, Colorado tick fever, and Borrelia miyamotoi infection.(1) Several of these diseases are transmitted by the same tick, and coinfections are occasionally seen. In particular, Ixodes species ticks are capable of transmitting the causative agents of Lyme disease (B burgdorferi and B mayonii), anaplasmosis (Anaplasma phagocytophilum), and babesiosis (Babesia species). These diseases are prevalent throughout the northeastern and upper Midwestern states and parts of the Pacific Northwest. Symptoms of the various tick-vectored diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A rapid tick-borne PCR panel can assist in identifying the pathogen, allowing treatment to be initiated. While Lyme disease due to B burgdorferi is best detected through 2-tiered serologic testing, acute ehrlichiosis, anaplasmosis, babesiosis, and B miyamotoi infection are best detected using molecular amplification assays. This tick-borne panel offers sensitive, specific, and rapid detection of the agents that cause these 4 diseases. For information on the specific diseases, see the individual test IDs.

Useful For: Evaluation of patients with suspected human monocytic ehrlichiosis, human granulocytic anaplasmosis, babesiosis, or Borrelia miyamotoi infection Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms

Interpretation: Borrelia miyamotoi: A positive result indicates the presence of B miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever. Ehrlichia/Anaplasma: Positive results indicate presence of specific DNA from Ehrlichia chaffeensis, E ewingii, E muris eauclairensis, or A phagocytophilum and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens, but it does not exclude the presence of the organism or active or recent disease. Since DNA of E ewingii is indistinguishable from that of E canis by this rapid PCR assay, a positive result for E ewingii/canis indicates the presence of DNA from either of these 2 organisms. Babesia: A positive result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results and clinical findings. A negative result indicates absence of detectable DNA from Babesia species in the specimen, but does not always rule-out ongoing babesiosis in a seropositive person, since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in the evaluation of a patient presenting with an acute febrile illness following tick
exposure include serologic tests for Lyme disease (B burgdorferi), and molecular detection (PCR) for 
ehrlichiosis/anaplasmosis. For patients who are past the acute stage of infection, serologic tests for these 
organisms should be ordered prior to PCR testing.

**Reference Values:**
Babesia species, MOLECULAR DETECTION, PCR  
Negative

Ehrlichia/Anaplasma, MOLECULAR DETECTION, PCR  
Negative

Borrelia miyamotoi, MOLECULAR DETECTION, PCR  
Negative

**Clinical References:** Caulfield AJ, Pritt BS: Lyme Disease Coinfections in the United States. Clin 

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**FFTIC 91273**  
**Ticlopidine, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Ticlopidine  
Synonym(s): Ticlid

Steady state peak plasma levels from patients on a 250 mg twice daily regimen: 0.22 ÁEâ€“2.1 mcg/mL (mean of 0.99) at 2 hours post dose.

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**FFTIL 57558**  
**Tilapia IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69  
Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5  
50.0-99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**  
<0.35 kU/L

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**TIMG 82891**  
**Timothy Grass, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are 
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from 
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE 
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the 
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for 
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and 
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of 
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and 
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and 
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to 
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to timothy grass Defining the allergen responsible 
for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or 
anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the 
specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**FFTIB**

91137 Tin, Blood

**Reference Values:**

Reference Range: <5.0 ng/mL

Toxic range not established.

**FFTIN**

91101 Tin, Serum

**Reference Values:**

Reference Range: <5.0 ng/mL

Toxic range has not been established.

Note: Whole blood is the preferred specimen for monitoring exposure to tin.

**FXTDS**

57733 Tissue Drug Screen

**Reference Values:**

Testing is complete. Report has been attached in Mayo Access.

**TISSR**

45444 Tissue Processing (Bill Only)

**Reference Values:**

This test is for billing purposes only. 
This is not an orderable test.
Tissue Transglutaminase Antibodies, IgA and IgG Profile, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms.

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for HLA DQ2 and/or DQ8) Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: The finding of tissue transglutaminase (tTG) IgA antibodies is specific for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is likely and the patient should undergo biopsy to confirm the diagnosis. The finding of tTG IgG antibodies may indicate a diagnosis of celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and the patient should undergo a biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of anti-tTG antibodies should begin to decrease within 6 to 12 months of onset of dietary therapy.

Reference Values:

<table>
<thead>
<tr>
<th>tTG ANTIBODY, IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.0 U/mL (negative)</td>
</tr>
<tr>
<td>4.0-10.0 U/mL (weak positive)</td>
</tr>
<tr>
<td>&gt;10.0 U/mL (positive)</td>
</tr>
<tr>
<td>Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>tTG ANTIBODY, IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.0 U/mL (negative)</td>
</tr>
<tr>
<td>6.0-9.0 U/mL (weak positive)</td>
</tr>
<tr>
<td>&gt;9.0 U/mL (positive)</td>
</tr>
<tr>
<td>Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Tissue Transglutaminase Antibody, IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type 1 diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Screening test for dermatitis herpetiformis, in conjunction with endomysial antibody test Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: The finding of tissue transglutaminase (tTG)-IgA antibodies is specific for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is likely and the patient should undergo biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of IgA-anti-tTG should begin to decrease within 6 to 12 months of onset of dietary therapy.

Reference Values:
- <4.0 U/mL (negative)
- 4.0-10.0 U/mL (weak positive)
- >10.0 U/mL (positive)

Reference values apply to all ages.

Tissue Transglutaminase Antibody, IgG, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

Useful For: For individuals with IgA deficiency: -Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8 -Screening test for dermatitis herpetiformis, in conjunction with endomysial antibody test -Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: The finding of tissue transglutaminase (tTG) IgG antibodies may indicate a diagnosis of celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and the patient should undergo a biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of tTG-IgG antibodies should begin to decrease within 6 to 12 months of onset of dietary therapy. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.
Reference Values:
<6.0 U/mL (negative)
6.0-9.0 U/mL (weak positive)
>9.0 U/mL (positive)
Reference values apply to all ages.


Titanium, Serum

Clinical Information: Titanium is the ninth most abundant element in the earth’s crust. Multiple oxidation states between 2+ and 4+ allow formation of a variety of compounds. There is no evidence that titanium is an essential element. Due in part to titanium’s oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic food-stuffs. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%), and the majority of ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lung. Titanium dust entering the respiratory tract is nonirritating and is almost completely nonfibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study, patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable serum titanium. While titanium concentrations are not a measure of toxicity, they are useful in determining whether implant breakdown is occurring. Serum titanium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring metallic prosthetic implant wear

Interpretation: Prosthesis wear is known to result in increased circulating concentration of metal ions. In the absence of an implant, circulating titanium is below 1 ng/mL. Modest increase (1.0-3.0 ng/mL) in serum titanium concentration is evident with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with titanium-based implant suggest prostheses wear. Increased serum titanium concentration in the absence of corroborating clinical information does not independently predict prostheses wear or failure.

Reference Values:
<2 ng/mL

TLE1 Immunostain, Technical Component Only

Clinical Information: Transducin-like enhancer of split proteins (TLE-1) associates with chromatin, specifically with histone H3. TLE1 is upregulated in early stages of cell differentiation and may have value in the diagnosis of synovial sarcoma, where it is positive in the majority of the cases. However, this marker is not entirely specific for synovial sarcoma, and results should be interpreted in the context of other clinicopathologic and immunophenotypic features.

Useful For: Aids in the identification of synovial sarcoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


TNF-alpha (TNF-a) Serum

Clinical Information: Cytokines have emerged as molecules of importance in the regulation of many immunologic processes in the cell. The ability to accurately measure quantitative and qualitative differences in cytokine production is becoming increasingly important to the understanding of normal and pathological processes.

Reference Values: <5.6 pg/mL


Tobramycin, Peak, Serum

Clinical Information: Tobramycin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities
include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of serum concentration during tobramycin therapy

**Interpretation:** Target peak concentrations depend on the type of infection being treated. Peak levels for most infections using conventional dosing are 3.0 to 12.0 mcg/mL. Prolonged exposure to peak concentrations exceeding 12.0 mcg/mL may lead to toxicity.

**Reference Values:**
- Therapeutic: 3.0-12.0 mcg/mL
- Toxic: >12.0 mcg/mL

**Clinical References:**

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**Tobramycin, Random, Serum**

**Clinical Information:** Tobramycin is an antibiotic used to treat life-threatening blood infections by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of serum concentration during tobramycin therapy This unit code is used whenever a specimen is submitted or collected without collection timing information. The phlebotomist should use this unit code if she or he does not know if this is a peak or trough specimen.

**Interpretation:** Target peak concentrations depend on the type of infection being treated. Goal trough levels should be below 2.0 mcg/mL. Concentrations refer to conventional (non-pulse) dosing. Prolonged exposure to either peak levels exceeding 12.0 mcg/mL or trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
- **TOBRAMYCIN, PEAK**
  - Therapeutic: 3.0-12.0 mcg/mL
  - Toxic: >12.0 mcg/mL

- **TOBRAMYCIN, TROUGH**
  - Therapeutic: <2.0 mcg/mL
  - Toxic: >2.0 mcg/mL

**Clinical References:**
**Tobramycin, Trough, Serum**

**Clinical Information:** Tobramycin is an antibiotic used to treat life-threatening blood infections by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequate clearance of tobramycin near the end of a dosing cycle

**Interpretation:** Goal levels depend on the type of infection being treated. Goal trough levels should be below 2.0 mcg/mL for conventional (nonpulse) dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
- Therapeutic: <2.0 mcg/mL
- Toxic: >2.0 mcg/mL

**Clinical References:**

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**Tocilizumab Quantitation, Serum**

**Clinical Information:** Tocilizumab is a recombinant humanized IgG1 kappa monoclonal antibody that targets the interleukin-6 (IL-6) receptor. By binding soluble and membrane-bound IL-6 receptors, it blocks the pro-inflammatory effects of IL-6 mediated signaling. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. Although a critical component of the immune response against infection, IL-6 is an important mediator in many autoimmune diseases. For example, IL-6 is produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis (RA). Studies in a variety of autoimmune diseases demonstrated that blocking IL-6 led to improved clinical outcomes. Tocilizumab is currently Food and Drug Administration-approved for the treatment of RA (moderate to severe), giant cell arteritis, systemic juvenile idiopathic arthritis (JIA), and polyarticular JIA. IL-6 is also a critical component of the cytokine release syndrome (CRS). CRS results from an overactive immune response and leads to significantly enhanced expression of multiple inflammatory cytokines. CRS can occur in a variety of situations, including autoimmune disease, infection, and immune therapies. Chimeric antigen receptor (CAR) T-cell therapy is approved for the treatment of large B-cell non-Hodgkin lymphomas and acute lymphoblastic leukemia. In this therapy, the patient’s T cells are isolated and genetically engineered to express chimeric antigen receptors, which target the tumor cells. Some patients experience CRS after the engineered T cells are re-administered; in some cases the magnitude of the CRS can be life-threatening with manifestations including hypotension, tachycardia, and multi-organ failure. Tocilizumab is approved for treatment of CRS associated with CAR T-cell therapy. It is also being investigated for treatment of CRS in other clinical situations. Pharmacokinetics of tocilizumab is characterized by nonlinear elimination, which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of tocilizumab elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab is also concentration-dependent and varies depending on the serum concentration.
concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.(1)

**Useful For:** Quantitation of tocilizumab

**Interpretation:** Measured concentrations of tocilizumab will be impacted by the route of administration, the dosage, and the time interval between drug administration and blood collection. Measured concentrations should be interpreted in the context of the last administered dose of tocilizumab.

**Reference Values:**
Tocilizumab limit of quantitation =0.5 mcg/mL


**Toluene as Hippuric Acid, Occupational Exposure, Urine**

**Reference Values:**
Creatinine: >50 mg/mL

Hippuric Acid is a metabolite of toluene and benzyl alcohol.

Normal (unexposed population):
Average 0.8 g/L

Exposed:

Biological Exposure Index (BEI):
1.6 g/g creatinine
(toluene exposure: end of shift)

Toxic:
Not established

**Toluene, Occupational Exposure, Blood**

**Reference Values:**
Units: mg/L

Normal (unexposed population): None detected

Exposed:

Biological Exposure Index (BEI): 0.05 mg/L (prior to last shift of workweek)

Biological Tolerance Value (BAT): 1.0 mg/L (end of exposure or end of shift)

Toxic:
Blood levels between 50 and 79 mg/L were found in people who died of acute toluene inhalation.

**Tomato IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of
food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Tomato, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to tomato Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Topiramate, Serum**

**Clinical Information:** Topiramate is a broad spectrum, antiepileptic drug used for various types of seizures, Lennox-Gastaut syndrome (a type of childhood onset epilepsy), and migraine prophylaxis. Topiramate blocks voltage-dependent sodium channels, potentiates gamma-aminobutyric acid (GABA) activity at some of the GABA receptors, and inhibits potentiation of the glutamate receptor and carbonic...
anhydrase enzyme, which all contribute to its antiepileptic and antimigraine efficacy. In general, topiramate shows favorable pharmacokinetics with good absorption (1-4 hours for the immediate-release formulation), low protein binding, and minimal hepatic metabolism. Elimination is predominantly renal and it is excreted unchanged in the urine with an elimination half-life of approximately 21 hours. As with other anticonvulsant drugs eliminated by the renal system, patients with impaired renal function exhibit decreased topiramate clearance and a prolonged elimination half-life. Serum concentrations of other anticonvulsant drugs are not significantly affected by the concurrent administration of topiramate with the exception of patients on phenytoin, whose serum concentrations can increase after the addition of topiramate. Other drug-drug interactions include the coadministration of phenobarbital, phenytoin, or carbamazepine, which can result in decreased topiramate concentrations. In addition, concurrent use of posaconazole and topiramate may result in the elevation of topiramate serum concentrations. Therefore, changes in cotherapy with these medications (phenytoin, carbamazepine, posaconazole, or phenobarbital) may require dose adjustment of topiramate and therapeutic drug monitoring could assist with this. The most common adverse drug effects associated with topiramate include: weight loss, loss of appetite, somnolence, dizziness, coordination problems, memory impairment, and paresthesia.

**Useful For:** Monitoring serum concentrations of topiramate Assessing compliance Assessing potential toxicity

**Interpretation:** Most individuals display optimal response to topiramate with serum levels 5.0 to 20.0 mcg/mL when used to control seizures. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Toxic levels have not been well established.

**Reference Values:**
Depends on clinical use:
- Anticonvulsant: 5.0-20.0 mcg/mL
- Psychiatric: 2.0-8.0 mcg/mL

**Clinical References:**

**TRCHG**

**ToRCH Profile IgG, Serum**

**Clinical Information:** Toxoplasma gondii: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs.
Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual and audiologic defects. Rubella: Rubella (German or 3-day measles) is a member of the Togavirus family, and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets, and the incubation period following exposure can range from 12 to 23 days. Infection is generally mild, self-limited and characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. Primary, in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, cardiovascular and ocular defects. The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. A total of 4 cases of rubella were reported to the Centers for Disease Control and Prevention (CDC) in 2011 without any cases of congenital rubella syndrome. Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States. However, immunity may wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella. Cytomegalovirus: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multi-organ failure. CMV is also responsible for congenital disease among newborns and is 1 of the ToRCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus [HSV]). CMV seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in children between the ages of 6 and 11 and adults over 80 years old, respectively. Herpes Simplex Virus Types 1 and 2: HSV types 1 and 2 are members of the Herpesviridae family and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction (PCR) or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. For example, the risk for reactivation is highest for HSV type 2 and the method of antiviral therapy may be different depending on the specific type of HSV causing disease. In addition, the results of HSV type specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.

**Useful For:** Determination of immune status of individuals to the rubella virus following vaccination or prior exposure As an indication of past or recent infection with Toxoplasma gondii, cytomegalovirus, or herpes simplex virus (HSV) Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

**Interpretation:** Toxoplasma gondii: A positive Toxoplasma IgG result is indicative of current or past infection with T gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG
during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to T gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of T gondii infection subsequent to the first negative specimen. Rubella: Positive: The presence of detectable IgG-class antibodies to rubella indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to rubella are considered immune. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies to rubella suggests no prior exposure to this virus or the lack of a specific immune response to immunization. Cytomegalovirus: Positive cytomegalovirus (CMV) IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional specimen for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are therefore considered susceptible to primary infection. Herpes Simplex Virus: The presence of IgG-class antibodies to herpes simplex virus (HSV) types 1 or 2 indicates previous exposure and does not necessarily indicate that HSV is the causative agent of an acute illness.

**Reference Values:**

**Toxoplasma ANTIBODY, IgG**

Negative

Toxoplasma IgG  
< or = 9 IU/mL (Negative)  
10-11 IU/mL (Equivocal)  
> or = 12 IU/mL (Positive)

**RUBELLA ANTIBODY, IgG**

Vaccinated: Positive (> or = 1.0 AI)  
Unvaccinated: Negative (< or = 0.7 AI)

**CYTOMEGALOVIRUS**

Negative

**HERPES SIMPLEX VIRUS (HSV), TYPE 1 AND TYPE 2 ANTIBODIES, IgG**

Herpes Simplex Virus (HSV) Type 1, IgG  
Negative

Herpes Simplex Virus (HSV) Type 2, IgG  
Negative

**Clinical Information:** Toxocariasis is a zoonotic parasitic disease caused by the nematode, Toxocara, of which there are 2 species: Toxocara canis and Toxocaracati. Toxocara eggs are shed in the feces of infected animals and, once in the environment, become infectious within 2 to 4 weeks. Humans are accidental hosts and become infected through ingestion of dirt or contaminated material containing Toxocara eggs. Although uncommon, individuals can also get toxocariasis by eating undercooked or raw meat from infected animals. Upon ingestion, Toxocara eggs hatch and larvae are released, which can penetrate the intestinal wall travel, through the bloodstream, and migrate to a variety of tissues (eg, liver, heart, lungs, brain, muscles, eyes). Although Toxocara larvae do not undergo any further development at these sites, they can cause severe local inflammatory reactions that are the basis of toxocariasis. While the majority of infected people do not have any symptoms, the 2 primary clinical presentations of toxocariasis are visceral larva migrans (visceral toxocariasis) and ocular larva migrans (ocular toxocariasis). Manifestations of toxocariasis reflect parasitic burden, immune response, and resulting inflammation. Symptoms of larva migrans may be characterized by Loffler syndrome (eg, fever, coughing, wheezing, abdominal pain), hepatomegaly, eosinophilia, or irreversible eye problems. Rarely, larvae migrate to the central nervous system (CNS), causing eosinophilic meningoencephalitis or granuloma formation. Larvae can also migrate to and penetrate the eye, resulting in ocular toxocariasis, which may lead to retinal scarring, decreased vision, and leukocoria. A recent Toxocara seroprevalence study in the United States showed that approximately 5% of the US population is infected with Toxocara. Globally, toxocariasis is found in many countries, and rates of prevalence can be as high as 40%, particularly in tropical regions where eggs remain viable in the soil. Children and adolescents under the age of 20, as well as dog owners, are at higher risk of infection. Diagnosis of Toxocara infections involves obtaining relevant clinical and exposure history and relies on antibody detection to Toxocara species. Eosinophilia may also be present, more commonly in visceral toxocariasis. Stool examination for ova and parasites is not useful since eggs are not excreted by humans, only by domestic animals. Currently, antibody testing is the only means of confirming a clinical diagnosis. The recommended serologic test for toxocariasis is an enzyme-linked immunosorbent assay (ELISA) using larval-stage antigens. However, a measureable titer does not distinguish between current and past Toxocara infection. Laboratory findings should be correlated with clinical history.

**Useful For:** Aiding in the diagnosis of Toxocara infection

**Interpretation:** Positive: IgG antibodies to Toxocara species detected, suggesting current or past infection. False-positive results may occur in patients with other helminth infections (eg, Ascaris lumbricoides, Schistosoma species, Strongyloides). Negative: No antibodies to Toxocara species detected. Repeat testing may be considered in patients presenting soon after possible exposure to Toxocara.

**Reference Values:**
Negative

Reference values apply to all ages.

**Clinical References:**
Toxoplasma gondii Antibodies (IgG, IgM), ELISA, CSF

**Interpretation:** Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

**Reference Values:**

Reference Range:
- IgG: <0.90
- IgM: <0.80

**INTERPRETIVE CRITERIA:**

- IgG:
  - <0.90: Antibody not detected
  - 0.9-1.09: Equivocal
  - >or=1.10: Antibody detected
- IgM:
  - <0.80: Antibody not detected
  - 0.80-0.99: Equivocal

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Toxoplasma gondii Antibody, IgG, Serum

**Clinical Information:** Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to T gondii. Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy progresses. Conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

**Useful For:** Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii. This test is not useful for diagnosing infection in infants younger than 6 months of age. In that age group, IgG antibodies usually are the result of passive transfer from the mother.

**Interpretation:** A positive Toxoplasma IgG result is indicative of current or past infection with
Toxoplasma gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to T gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of T gondii infection subsequent to the first negative specimen. Recent or acute infection with T gondii can be evaluated with TXM / Toxoplasma gondii Antibody, IgM, Serum. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by polymerase chain reaction (PCR) analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR, Varies). For additional confirmation of a diagnosis, the Food and Drug Administration (FDA) issued a Public Health Advisory (7/25/1997) suggesting that sera found to be positive/equivocal for T gondii IgM antibody be sent to a Toxoplasma reference laboratory. Recommended laboratories included the Centers for Disease Control and Prevention (CDC) or Jack Remington MD, Palo Alto Medical Foundation, 860 Bryant St., Palo Alto, CA 94301.

Reference Values:
Toxoplasma ANTIBODY, IgG
Negative

Toxoplasma IgG
< or = 9 IU/mL (Negative)
10-11 IU/mL (Equivocal)
> or = 12 IU/mL (Positive)
Reference values apply to all ages.

approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

Useful For: Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii IgG is not useful for diagnosing infection in infants younger than 6 months of age. IgG antibodies in this age group usually are the result of passive transfer from the mother.

Interpretation: Active toxoplasmosis is suggested by the presence of IgM-class antibodies, but elevated anti-IgM titers may be absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by polymerase chain reaction (PCR) analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR, Varies). For confirmation of toxoplasmosis, the FDA issued a Public Health Advisory (07/25/1997) that recommends that sera found to be positive for T gondii IgM antibodies should be sent to a Toxoplasma reference laboratory. A single negative result should not be used to rule-out toxoplasmosis and repeat testing is recommended for patients at high risk for infection. IgG is only indicative of previous exposure to Toxoplasma (recent or past). A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Seroconversion from negative to positive IgG is indicative of recent T gondii infection.

Reference Values:
Toxoplasma IgM
Negative

Toxoplasma IgG
Negative

Toxoplasma IgG Value
< or =9 IU/mL (Negative)
10-11 IU/mL (Equivocal)
> or =12 IU/mL (Positive)
Reference values apply to all ages.


Toxoplasma gondii Antibody, IgM, Serum

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to Toxoplasma gondii. Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. Transplacental transmission of the...
parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual and audiologic defects.

**Useful For:** Detection of recent infection with *Toxoplasma gondii*

**Interpretation:** Active toxoplasmosis is suggested by the presence of IgM-class antibodies, but elevated anti-IgM titers may be absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of *Toxoplasma gondii* DNA by polymerase chain reaction (PCR) analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / *Toxoplasma gondii*, Molecular Detection, PCR, Varies). For confirmation of toxoplasmosis, the FDA issued a Public Health Advisory (07/25/1997) that recommends that sera found to be positive for *Toxoplasma gondii* IgM antibodies should be sent to a Toxoplasma reference laboratory. A single negative result should not be used to rule-out toxoplasmosis and repeat testing is recommended for patients at high risk for infection.

**Reference Values:**
- Negative
- Reference values apply to all ages.

**Clinical References:**

**TOXB 62977**

**Toxoplasma gondii, Molecular Detection, PCR, Blood**

**Clinical Information:** *Toxoplasma gondii* is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, *T. gondii* can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to *T. gondii*.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero.
infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Detection of T gondii DNA by PCR has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis. When performed on blood, it may detect circulating parasite DNA and thus confirm or support the results of serologic testing. PCR testing on peripheral blood has been used successfully to detect cases of ocular toxoplasmosis(2) as well as invasive disease in allogeneic stem cell recipients.(3,4) However, blood may not be a sensitive specimen for detecting organ specific disease (eg, ocular or cerebral toxoplasmosis). In this case, other specimens (eg, ocular fluid, CSF, fresh tissue) should be considered (order PTOX / Toxoplasma gondii, Molecular Detection, PCR).

**Useful For:** Supporting the diagnosis of active toxoplasmosis, particularly in immunocompromised individuals

**Interpretation:** A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA, but do not exclude the presence of organism or active or recent disease.

**Reference Values:**

Negative

**Clinical References:**


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**PTOX**

**81795**

**Toxoplasma gondii, Molecular Detection, PCR, Varies**

**Clinical Information:** Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Serology is the traditional method for diagnosing toxoplasmosis and ascertaining the previous exposure history of the host. However, serology may be unreliable or challenging to interpret in immunocompromised patients and in suspected intrauterine infection. Detection of T gondii DNA by PCR has proven to be a
TOXO
70569

Toxoplasma Immunostain, Technical Component Only

Clinical Information: Immunohistochemical staining for Toxoplasma gondii can help identify the organisms in the cytoplasm of infected cells. T gondii is a sporozoan that lives as an intracellular parasite in various tissues of vertebrates. T gondii is transmitted via raw or undercooked meat, contaminated soil, or by direct contact. Pregnant women and immunosuppressed patients are at highest risk for infection.

Useful For: Identification of Toxoplasma gondii infection

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

TP53 Gene Somatic Mutation Pre-Analysis Cell Sorting, Varies

Clinical Information: Patients with chronic lymphocytic leukemia (CLL) have variable disease course influenced by a series of tumor biologic factors. The presence of chromosomal 17p- or TP53 gene variation confers a very poor prognosis to a subset of CLL patients, both at time of initial diagnosis as well as at disease progression, or in the setting of therapeutic resistance. TP53 gene variant status in CLL has emerged as the single most predictive tumor genetic abnormality associated with adverse outcome and poor response to standard immunochemotherapy; however, patients can be managed with alternative therapeutic options.

Useful For: Determination of B-cell content and confirmation the presence of a clonal B-cell
population evaluating chronic lymphocytic leukemia patients prior to TP53 variant analysis

**Interpretation:** Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

**Reference Values:**
Only orderable as a reflex. For more information see P53CA / Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9, Varies.

**Clinical References:**

**TP53 Gene, Li Fraumeni Syndrome, Full Gene Analysis, Varies**

**Clinical Information:** Li-Fraumeni syndrome (LFS) is a rare autosomal dominant hereditary cancer syndrome associated with germline variants in the TP53 (also p53) gene. LFS is predominantly characterized by sarcoma (osteogenic, chondrosarcoma, rhabdomyosarcoma), young-onset breast cancer, brain cancer (glioblastoma), hematopoietic malignancies, and adrenocortical carcinoma in affected individuals. LFS is highly penetrant; the risk for developing an invasive cancer is 50% by age 30 and 90% by age 70 with many individuals developing multiple primary cancers. Childhood cancers are also frequently observed and typically include soft-tissue sarcomas, adrenocortical tumors, and brain cancer. Other reported malignancies include melanoma, Wilms tumor, kidney tumors, gonadal germ cell tumor, pancreatic cancer, gastric cancer, choriocarcinoma, colorectal cancer, prostate cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, and thyroid cancer. There are published criteria for the use in establishing a clinical diagnosis of classic Li-Fraumeni syndrome and Li-Fraumeni-like (LFL) syndrome that include the above features listed. A larger percentage of families that meet the classic LFS criteria are predicted to have a detectable variant within the TP53 gene than families that meet the less strict LFL criteria (Birch's and Eeles' definitions).

**Useful For:** Confirmation of suspected clinical diagnosis of Li-Fraumeni syndrome or Li-Fraumeni-like syndrome Identification of familial TP53 variant to allow for predictive testing in family members Predictive testing of an asymptomatic child is not recommended.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
2. Lindor NM, McMaster ML, Lindor CJ, Greene MH, National Cancer Institute,
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to tragacanth Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3 3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Tramadol and Metabolite, Random, Urine**

**Clinical Information:** Tramadol, a centrally acting opioid analgesic, is utilized in the treatment of moderate to moderately severe pain. Tramadol acts as an opiate agonist through the binding of the parent drug and its O-desmethyl (M1) metabolite to mu-opioid receptors and through the weak inhibition of norepinephrine and serotonin reuptake. The active metabolite, O-desmethyltramadol, is a considerably more potent mu-opioid receptor agonist than its parent drug. In urine, approximately 30% of tramadol is excreted as unchanged drug, while approximately 60% is excreted as metabolites (N- and O-desmethyltramadol). The half-life of tramadol and O-desmethyltramadol is approximately 7 hours.

**Useful For:** Monitoring of compliance utilizing tramadol Detection and confirmation of the illicit use of tramadol

**Interpretation:** The presence of tramadol or O-desmethyltramadol levels of 25 ng/mL or higher is a strong indicator that the patient has used tramadol.

**Reference Values:**
Cutoff: 25 ng/mL

**Clinical References:**

**Transcription Factor E3 (TFE3) Immunostain, Technical Component Only**

**Clinical Information:** Transcription factor E3 (TFE3) is a member of the microphthalmia transcription factor (MiTF)/TFE family of helix-loop-helix transcription factors. TFE3 overexpression is observed in TFE translocation-associated renal cell carcinoma and alveolar soft part sarcoma.

**Useful For:** Assessment of transcription factor E3 expression

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Transferrin, Serum**

**Clinical Information:** Transferrin is a glycoprotein with a molecular weight of 79570 daltons. It consists of a polypeptide strand with 2 N-glycosidically linked oligosaccharide chains and exists in numerous isoforms. The rate of synthesis in the liver can be altered in accordance with the body's iron requirements and iron reserves. Transferrin is the iron transport protein in serum. In cases of iron deficiency, the degree of transferrin saturation appears to be an extremely sensitive indicator.
The ferritin levels are depressed when there is a deficiency of storage iron. In sideropenia, an iron deficiency can be excluded if the serum transferrin concentration is low, as in inflammation or less commonly, in cases of ascorbic acid deficiency. In screening for hereditary hemochromatosis, transferrin saturation provides a better indication of the homozygous genotype than ferritin. The treatment of anemia with erythropoietin in patients with renal failure is only effective when sufficient depot iron is present. The best monitoring procedure is to determine transferrin saturation during therapy. Transferrin saturation in conjunction with ferritin gives a conclusive prediction of the exclusion of iron overloading in patients with chronic liver disease.

**Useful For:** Screening for chronic iron overload diseases, particularly hereditary hemochromatosis

**Interpretation:** Serum iron, total iron-binding capacity (TIBC), and percent saturation are useful only in screening for chronic iron overload diseases, particularly hereditary hemochromatosis. Although serum iron, TIBC, and percent saturation are widely used for the diagnosis of iron deficiency, serum ferritin is a much more sensitive and reliable means of demonstrating iron deficiency. In hereditary hemochromatosis, serum iron is usually above 150 mcg/dL and percent saturation exceeds 60%. In advanced iron overload states, the percent saturation often exceeds 90%.

**Reference Values:**
- 200-360 mg/dL

**Clinical References:**
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to trees in panel #1, defining the allergen responsible for eliciting signs and symptoms, identifying allergens responsible for allergic disease and/or anaphylactic episode, confirming sensitization prior to beginning immunotherapy, investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens, testing for IgE antibodies in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to trees in panel #3 Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Tree Panel #4, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to trees in panel #4 Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To
investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<td>2</td>
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<tr>
<td>6</td>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**TREPE 70571**

**Treponema pallidum Immunostain, Technical Component Only**

**Clinical Information:** Syphilis is caused by infection with the spirochete Treponema pallidum. Transmission of T pallidum occurs via penetration of the spirochetes through mucosal membranes and abrasions on epithelial surfaces. This test will identify T pallidum, however it also cross-reacts with other spirochetes.

**Useful For:** Identification of Treponema pallidum in tissues

**Interpretation:** This test does not include pathologist interpretation; only technical performance of the stain is performed. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Triazolam (Halcion)**

**Reference Values:**
Reference Range: 5.0 - 20.0 ng/mL

---

**Trichinella Antibody, Serum**

**Clinical Information:** Trichinosis is an infection by the nematode parasite, *Trichinella spiralis*. The infection is acquired by ingestion of larvae in inadequately cooked, contaminated meat, especially pork, bear, and walrus meat. After ingestion, acid-pepsin digestion in the stomach liberates the larvae, which develop into adult worms in the small intestine. After fertilization, the female worm produces larvae that penetrate the mucosa and seed the skeletal muscles via the blood stream. The larvae coil and encyst in muscle fibers, remaining viable for up to several years. Diarrhea is the most common symptom associated with intestinal infection with adult worms. Fever, periorbital swelling, muscle pain and swelling, pulmonary symptoms, and rash develop during systemic invasion by the larvae.

**Useful For:** As an adjunct in the diagnosis of trichinosis

**Interpretation:** A positive enzyme-linked immunosorbent assay result suggests current infection with *Trichinella spiralis*. Serology should be used in conjunction with clinical, epidemiologic, and other laboratory tests to establish the correct diagnosis. The number of individuals showing positive results may vary significantly between populations and geographic regions.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

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**Trichloroacetic Acid, Urine**

**Reference Values:**
Creatinine: >50 mg/dL

Trichloroethane Exposure:
- Normal (unexposed population): None detected
- Exposed:
  - Biological Exposure Index (BEI):
    - 10 mg/L (end of workweek)
  - Toxic: Not established

Trichloroethylene Exposure:
- Normal (unexposed population): None detected
- Exposed:
  - Biological Exposure Index (BEI):
    - 100 mg/g creat (end of workweek)

**Biological Tolerance Value (BAT):**
100 mg/L (end of exposure or end of shift, or after several shifts for long-term exposure)
Trichoderma viride, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Trichoderma viride Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>

**TVRNA**

**Trichomonas vaginalis by Nucleic Acid Amplification, Varies**

**Clinical Information:** Trichomonas vaginalis (TV) is a protozoan parasite that commonly infects the genital tract of men and women. It is now considered to be the most common curable sexually transmitted infection (STI) agent, with an estimated 3.7 million infected individuals in the United States.(1-4) Although up to 70% of infected individuals are asymptomatic, infections may be associated with vaginitis, urethritis, and cervicitis in women, and urethritis and prostatitis in men.(3) Patients that are infected with T vaginalis have an increased risk of acquiring other sexually transmitted infections such as HIV, while infections in pregnant women are associated with premature labor, low birth-weight offspring, premature rupture of membranes, and posthysterectomy/postabortion infection.(3) Symptoms of T vaginalis overlap considerably with other sexually transmitted infections; therefore, laboratory diagnosis is required for definitive diagnosis. The most commonly used method for detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture.(5) Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods.(5) Culture is also technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the Aptima T vaginalis assay, offer the highest sensitivity and specificity for detection of trichomoniasis. The Aptima test utilizes target capture, transcription-mediated amplification (TMA), and hybridization protection assay (HPA) technologies for detection of T vaginalis ribosomal RNA (rRNA).

**Useful For:** Detection of Trichomonas vaginalis in female patients

**Interpretation:** A positive result is considered indicative of current or recent Trichomonas vaginalis infection (trichomoniasis).

**Reference Values:**

Negative


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**MTRNA**

**Trichomonas vaginalis, Nucleic Acid Amplification, Varies**

**Clinical Information:** Trichomonas vaginalis (TV) is a protozoan parasite that commonly infects the genital tract of men and women. It is now considered to be the most common curable sexually transmitted infection (STI) agent, with an estimated 3.7 million infected individuals in the United States.(1-4) Although up to 70% of infected individuals are asymptomatic, infections may be associated with vaginitis, urethritis, and cervicitis in women, and urethritis and prostatitis in men.(3) Patients that are infected with T vaginalis have an increased risk of acquiring other sexually transmitted infections such as HIV, while infections in pregnant women are associated with premature labor, low birth-weight offspring, premature rupture of membranes, and post-hysterectomy/post-abortion infection.(3) Symptoms of T vaginalis overlap considerably with other sexually transmitted infections; therefore, laboratory diagnosis is required for definitive diagnosis. The most commonly used method for detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture.(5) Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods.(5) Culture is technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the Aptima T vaginalis assay, offer high sensitivity and specificity for detection of trichomoniasis. The Aptima test utilizes target capture, transcription-mediated amplification (TMA), and hybridization protection assay (HPA) technologies for detection of T vaginalis ribosomal RNA (rRNA).
Useful For: Detection of Trichomonas vaginalis in urine and male patient specimens

Interpretation: A positive result is considered indicative of current or recent Trichomonas vaginalis infection (trichomoniasis).

Reference Values:
Negative


FFTMV

Trichophyton Mentagrophytes (var interdigitale) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

TCPT

Trichophyton rubrum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Trichophyton rubrum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
Triglycerides, Body Fluid

Clinical Information: Triglyceride concentration in body fluids is correlated to the presence of chylomicrons and can be useful when diagnosing chylous effusion or differentiating from pseudochylous effusion.(1) Chylous effusions are characterized by the presence of chyle which contains chylomicrons circulating through the lymphatic system. Pseudochylous effusions do not have chylomicrons. These fluids have a milky appearance and can be confused with chylous effusions. While chylous effusions often have elevated triglyceride concentrations and decreased cholesterol concentrations, identification of chylomicrons is considered the gold standard for the diagnosis.

Pleural fluid: Chylothorax is the name given to pleural effusions containing chylomicrons. They develop when chyle accumulates from disruption of the lymphatic system, often the thoracic duct, caused mainly by malignancy or trauma.(1) Lymph contains chylomicron rich chyle characterized by high concentrations of triglycerides. Pseudochylous effusions are the name given to milky appearing effusions that do not contain lymphatic contents but rather form gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema and by definition the effluent contains high concentrations of cholesterol.(2)

Peritoneal fluid: Chylous ascites is the name given to peritoneal effusions containing chylomicrons. Obstruction of lymph flow causing leakage from dilated subserosal lymphatics, exudation through the walls of retroperitoneal megalymphatics, and direct leakage of chyle due to a lymphoperitoneal fistula have been proposed as possible mechanisms causing chylous ascites.(3) Elevated triglyceride concentrations have the best correlation with detection of chylomicrons, while cholesterol is not useful at predicting the presence or absence of chylomicrons.

Useful For: Distinguishing between chylous and nonchylous effusions Measurement of triglycerides in body fluids as a surrogate for chylomicrons

Interpretation: Pleural fluid triglyceride concentrations over 110 mg/dL are consistent with a chylous effusion. Triglyceride concentrations below 50 mg/dL are usually not due to chylous effusions.(1) Peritoneal fluid triglyceride concentrations over 187 mg/dL are most consistent with chylous effusion.(3)

Reference Values: An interpretive report will be provided

**TRIGC**

**Triglycerides, CDC, Serum**

**Reference Values:**
Only orderable as part of a profile. For more information see LMPP / Lipoprotein Metabolism Profile, Serum.

**TRIGN**

**Triglycerides, Non-Fasting, Serum**

**Clinical Information:** Triglycerides are esters of the trihydric alcohol glycerol with 3 long-chain fatty acids. They are partly synthesized in the liver and partly derived from the diet. Increased plasma triglyceride levels are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or be associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (eg, prednisone). Since cholesterol and triglycerides can vary independently, measurement of both is more meaningful than the measurement of cholesterol only. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

**Useful For:** Evaluation of risk factors in individuals with elevated cholesterol values

**Interpretation:** In the presence of other coronary heart disease risk factors, both borderline-high (150-199 mg/dL) and high values (>200 mg/dL) require attention. Triglyceride concentrations greater than 1,000 mg/dL can lead to abdominal pain and may be life-threatening due to chylomicron-induced pancreatitis.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Non-HDL cholesterol) in adults ages 18 and up:

TRIGLYCERIDES

Males
- <200 mg/dL
- <175 mg/dL

Females
- <175 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2 to 17:

TRIGLYCERIDES

2-9 years:
- Acceptable: <75 mg/dL
- Borderline high: 75-99 mg/dL
- High: > or =100 mg/dL

10-17 years:
- Acceptable: <90 mg/dL
- Borderline high: 90-129 mg/dL
- High: > or =130 mg/dL

**Clinical References:**
**Triglycerides, Serum**

**Clinical Information:** Triglycerides are esters of the trihydric alcohol, glycerol, with 3 long-chain fatty acids. They are partly synthesized in the liver and partly derived from the diet. Increased plasma triglyceride levels are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or be associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (e.g., prednisone). Since cholesterol and triglycerides can vary independently, measurement of both is more meaningful than the measurement of cholesterol only.

**Useful For:** Evaluation of risk factors in individuals with elevated cholesterol values

**Interpretation:** In the presence of other coronary heart disease risk factors, both borderline-high (150-199 mg/dL) and high values (>200 mg/dL) require attention. Triglyceride concentrations above 1,000 mg/dL can lead to abdominal pain and may be life-threatening due to chylomicron-induced pancreatitis. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

**Reference Values:**

The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Non HDL cholesterol) in adults ages 18 and up:

TRIGLYCERIDES
Normal: <150 mg/dL
Borderline high: 150-199 mg/dL
High: 200-499 mg/dL
Very high: > or =500 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2 to 17:

TRIGLYCERIDES
2-9 years:
Acceptable: <75 mg/dL
Borderline high: 75-99 mg/dL
High: > or =100 mg/dL
10-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

**Clinical References:**

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**Trimethoprim, Serum**

**Clinical Information:** Trimethoprim is coadministered with sulfamethoxazole for prophylaxis or treatment of bacterial infections. These agents are used to treat a variety of infections including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients such as...
HIV-positive individuals. Trimethoprim has a wide therapeutic index and dose-dependent toxicity. Trimethoprim accumulates in patients with renal failure. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Accordingly, routine drug monitoring is not indicated in all patients.

**Useful For:** Monitoring trimethoprim therapy to ensure drug absorption, clearance, or compliance

**Interpretation:** Most patients will display peak steady state serum concentrations more than 2.0 mcg/mL when the specimen is collected at least 1 hour after an oral dose. Target concentrations may be higher depending on the intent of therapy.

**Reference Values:**
>2.0 mcg/mL

**Clinical References:**

---

**Trimipramine, Serum**

**Clinical Information:** Trimipramine is a tricyclic antidepressant with additional anxiety-reducing sedative activity. Daily dosages for adults range from 50 mg to 300 mg and are usually divided into 2 to 3 doses per day. Therapeutic ranges are based on serum samples collected at trough (ie, immediately before the next dose). Peak serum concentrations are typically achieved after 1 to 6 hours post dosage. Common adverse effects include hypotension, tachycardia, constipation, dizziness, somnolence, and blurred vision. Risk of toxicity increases when concentrations exceed 500 ng/mL. Serious adverse effects include coma, seizures, and QRS prolongation with ventricular dysrhythmias.

**Useful For:** Monitoring trimipramine concentration during therapy Evaluating potential trimipramine toxicity May aid in evaluating patient compliance

**Interpretation:** Most individuals display optimal response to trimipramine with serum levels of 150 to 300 ng/mL. Risk of toxicity is increased with trimipramine levels above 500 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

**Reference Values:**
Therapeutic concentration: 150-300 ng/mL
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**

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**Triosephosphate Isomerase Enzyme Activity, Blood**

**Clinical Information:** Triosephosphate isomerase (TPI) converts dihydroxyacetone phosphate (DHAP) to glyceraldehyde 3-phosphate (G3P) during glycolysis. Clinically significant TPI deficiency
(OMIM #615512, autosomal recessive) is rare and classically manifests as a severe multisystem disorder with early hemolytic anemia and progressive neurologic impairment in infancy. Other clinical features include motor impairment, diaphragm paralysis, cardiomyopathy, and susceptibility to infections. Some cases have isolated hemolytic anemia.

**Useful For:** Evaluating individuals with chronic nonspherocytic hemolytic anemia Evaluating individuals with early onset neurologic impairment Genetic counseling for families with triosephosphate isomerase (TPI) deficiency

**Interpretation:** Clinically significant hemolytic anemias due to triosephosphate isomerase (TPI) deficiency are associated with activity levels less than 30% of mean normal. Heterozygotes usually show approximately 50% of mean normal activity and are clinically unaffected.

**Reference Values:**
Only available as part of a profile. For more information see:
- HAEV1 / Hemolytic Anemia Evaluation, Blood
- EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 1033-1363 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**

---

**Triosephosphate Isomerase Enzyme Activity, Blood**

**Clinical Information:** Triosephosphate isomerase (TPI) converts dihydroxyacetone phosphate (DHAP) to glyceraldehyde 3-phosphate (G3P) during glycolysis. Clinically significant TPI deficiency (OMIM #615512, autosomal recessive) is rare and classically manifests as a severe multisystem disorder with early hemolytic anemia and progressive neurologic impairment in infancy. Other clinical features include motor impairment, diaphragm paralysis, cardiomyopathy, and susceptibility to infections. Some cases have isolated hemolytic anemia.

**Useful For:** Evaluating individuals with chronic nonspherocytic hemolytic anemia Evaluating individuals with early onset neurologic impairment Genetic counseling for families with triosephosphate isomerase deficiency

**Interpretation:** Clinically significant hemolytic anemias due to triosephosphate isomerase deficiency are associated with activity levels below 30% of mean normal. Heterozygotes usually show approximately 50% of mean normal activity and are clinically unaffected.

**Reference Values:**
> or =12 months: 1033-1363 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**
**Clinical Information:** The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. They are considered the most common of the neurogenetic storage disorders with incidences ranging from 1.3 to 7 per 100,000 live births. Clinically they are characterized by vision loss, seizures, mental regression, behavioral changes, movement disorders, and the accumulation of autofluorescent storage material in the brain and tissues. Although at least 12 different genes have been identified, the NCL have traditionally been categorized based on the age of onset of symptoms: infantile, late-infantile, juvenile, and adult. Infantile and late-infantile NCL are caused primarily by defects in PPT1 and TPP1, respectively. Tissue damage is selective for the nervous system and many patients die in the first decade of life due to central nervous system degeneration. Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age 2 years. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits (GROD) in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. Infantile NCL has an incidence of 1 in 20,000 in Finland and is rare elsewhere. The late infantile form of NCL (CLN2) is primarily caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss, and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. For other patients suspected of having an NCL, the molecular genetic test NCLGP / Neuronal Cereoid Lipofuscinosis (Batten Disease) Gene Panel, Varies is available.

**Useful For:** Evaluation of patients with clinical presentations suggestive of neuronal ceroid lipofuscinoses (NCL) Aids in the differential diagnosis of infantile and late infantile NCL This test is not useful for detecting carrier status of NCL.

**Interpretation:** Tripeptidyl peptidase 1 (TPP1) enzyme activity or palmitoyl-protein thioesterase 1 (PPT1) enzyme activity below 5 nmol/hour/mg of protein is highly suggestive of late-infantile and infantile neuronal ceroid lipofuscinoses (NCL), respectively.

**Reference Values:**

<table>
<thead>
<tr>
<th>TRIPEPTIDYL PEPTIDASE 1</th>
<th>PALMITOYL-PROTEIN THIOESTERASE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>85-326 nmol/hour/mg protein</td>
<td>20-93 nmol/hour/mg protein</td>
</tr>
</tbody>
</table>

strain for selection of CCR5 co-receptor antagonist therapy, when a patient's HIV-1 viral load is \( > \) or \( \geq \) 1,000 copies/mL.

**Interpretation:** CCR5 Tropic (R5) HIV-1 Virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1 Virus uses CXCR4 to enter CD4+ cells. DUAL/MIXED Tropic (D/M) HIV-1 Dual-tropic viruses can use either CCR5 or CXCR4 to enter CD4+ cells. Mixed-tropic populations contain viruses with two or more tropisms. Non-reportable Co-receptor tropism could not be determined by the Trofile assay. Common causes of a non-reportable result are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

**Tropheryma whipplei, Molecular Detection, PCR, Blood**

**Clinical Information:** Whipple disease is a chronic, systemic illness that, in the majority of cases, involves the small intestine and its lymphatic drainage. The disease primarily affects middle-aged individuals, with a peak incidence in the third and fourth decades of life. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillar backillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple-associated bacillus has been difficult because of these limitations. Recently, molecular techniques using polymerase chain reaction and nucleotide sequencing allowed classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

**Useful For:** Aiding in the diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases, using whole blood specimens

**Interpretation:** A positive result indicates the presence of Tropheryma whipplei DNA. A negative result indicates the absence of detectable T whipplei DNA, but does not negate the presence of the organism and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers or probes, or the presence of T whipplei DNA in quantities less than the limit of detection of the assay.

**Reference Values:** Not applicable

**Clinical References:**
1. Ramzan NN, Loftus E Jr, Burgart LJ, et al: Diagnosis and monitoring of

**Tropheryma whipplei, Molecular Detection, PCR, Varies**

**Clinical Information:** Whipple disease is a chronic, systemic illness that in the majority of cases involves the small intestine and its lymphatic drainage. The disease primarily affects middle-aged individuals, with a peak incidence in the third and fourth decades. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple associated bacillus has been difficult because of these limitations. Recently, molecular techniques using polymerase chain reaction and nucleotide sequencing allowed classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

**Useful For:** Aiding in the diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases, using tissue or fluid specimens

**Interpretation:** A positive result indicates the presence of Tropheryma whipplei DNA. A negative result indicates the absence of detectable T whipplei DNA, but does not negate the presence of the organism and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers or probes, or the presence of T whipplei DNA in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Tropomyosin Receptor Kinase (TRK) Immunostain, Technical Component Only**

**Clinical Information:** Neurotrophic tyrosine receptor kinase (NTRK) is a family of 3 proto-oncogenes including NTRK1, NTRK2, and NTRK3 which encode TRKA, TRKB, and TRKC proteins. Tropomyosin receptor kinase (TRK) immunohistochemistry may be used as a screen for identifying NTRK rearrangements and may be particularly helpful in driver-negative advanced malignancies such as secretory carcinoma, congenital infantile fibrosarcoma and lipofibromatosis-like neural tumors. Screening for NTRK rearranged tumors is important as patients have been shown to respond to TRK inhibitor therapy.

**Useful For:** Helpful in the screening for neurotrophic tyrosine receptor kinase (NTRK) rearranged tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is provided.
available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


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**TPNI**

81767

**Troponin I, Serum**

**Clinical Information:** Troponin is a complex that regulates the contraction of striated muscle. It consists of 3 subunits (C, T, and I) that are located periodically along the thin filament of the myofibrils. Troponin I inhibits actomyosin ATPase. Troponin I is an inhibitory protein and exhibits in 3 isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle. The cardiac form of troponin I has 31 amino acid residues on its N-terminal, not present in the skeletal forms, which allow for specific polyclonal and monoclonal antibody development. The cardiac specificity of this isoform improves the accuracy of diagnosis in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury. Troponin I is the only troponin isotope present in the myocardium and is not expressed during any developmental stage in skeletal muscle. Troponin I is released into the bloodstream within hours of the onset of symptoms of myocardial infarction or ischemic damage. It can be detected at 3 to 6 hours following onset of chest pain with peak concentrations at 12 to 16 hours, and remains elevated for 5 to 9 days.

**Useful For:** Exclusion diagnosis of acute myocardial infarction

**Interpretation:** There are, on occasions, elevations of cardiac troponin T (cTnT) which we use clinically which can be due to skeletal muscle disease. One way to unmask such elevations is to measure cardiac troponin I (cTnI), which will be normal in that circumstance. In addition, at times there are interferences that can cause spurious increases or decreases in cTnI values. Conceptually, these same interferences can occur with cTnI but in any given case, the likelihood of having both assays be confounded in that way is highly unusual. Thus, potential false-positives would be unmasked by a normal cTnI and false-negatives by an elevated value. A reference range study was conducted using the ADVIA Centaur TnI-Ultra assay based on guidance from the Clinical and Laboratory Standards Institute (CLSI) Protocol C28-A2.25. The study, which used 1,845 fresh serum, lithium heparin plasma, and EDTA plasma samples from 648 apparently healthy individuals ranging from 17 to 91 years of age, demonstrated a 99th percentile of 0.04 ng/mL (mcg/L).(1)

**Reference Values:**

< or =0.04 ng/mL

Reference values have not been established for patients <17 years of age.


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**TRPS**

65832

**Troponin T, 5th Generation, Plasma**

**Clinical Information:** Troponin T is a myofibrillar protein found in striated musculature. There are
2 types of myofilament: a thick filament containing myosin and a thin filament consisting of 3 different proteins, namely actin, tropomyosin, and troponin. Troponin is itself a complex of 3 protein subunits, which are termed troponin T, troponin I, and troponin C: 

- Troponin T binds the troponin complex to tropomyosin 
- Troponin I inhibits actomyosin ATPase in relation to the calcium concentration 
- Troponin C has 4 binding sites for calcium and mediates calcium dependency 

Troponin T is found in free cytosol and structurally bound protein. The unbound pool of troponin T is the source of early protein release in myocardial damage. Troponin T is released from the structural elements at a later stage, corresponding to the degradation of myofibrils that occurs in irreversible myocardial damage. Troponin T becomes elevated 2 to 4 hours after the onset of myocardial necrosis and can remain elevated for up to 14 days, or even longer on occasion. The most common cause of cardiac injury is myocardial ischemia, ie, acute myocardial infarction. These patients are known to have an adverse short- and long-term prognosis compared to patients with unstable angina and no elevation of troponin T. Many of these patients, especially those with troponin T elevations above 30 ng/L, benefit from an aggressive strategy with anticoagulation and an invasive interventional strategy.

**Useful For:** Aiding in the exclusion of the diagnosis of acute coronary syndrome in a single plasma specimen. Aiding in the diagnosis of acute coronary syndrome. Monitoring acute coronary syndromes and estimating prognosis. Possible utility in monitoring patients with nonischemic causes of cardiac injury.

**Interpretation:** Values for healthy adults, based upon available literature and clinical guidelines, are 10 ng/L or less for women and 15 ng/L or less for men. For patients who present with suspected acute coronary syndromes, troponin T values greater than the reference interval with a rising (> or =10 ng/L over 2 hours or > or =12 ng/L over 6 hours) pattern are highly suggestive of acute cardiac injury. Decreasing values are indicative of recent cardiac injury. Serial measurement is highly recommended for the diagnosis or exclusion of acute coronary syndromes. Troponin T values greater than the reference interval are associated with adverse events in patients with ischemic heart disease and many other clinical situations. Clinical judgment is necessary to distinguish patients who have ischemic heart disease from those who do not.

**Reference Values:**
- Males: < or =15 ng/L
- Females: < or =10 ng/L

**Clinical References:**

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**Trout, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to trout. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of...
allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Trypanosoma cruzi IgG Antibody, Lateral Flow Assay, Serum**

**Clinical Information:** Chagas disease (American trypanosomiasis) is an acute and chronic infection caused by the protozoan hemoflagellate, Trypanosoma cruzi endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma but may also be transmitted by blood transfusion, organ transplantation, vertically from mother to fetus, and food ingestion. The acute febrile infection is frequently undiagnosed and often resolves spontaneously. Diagnosis of acute T cruzi infection is most frequently confirmed by microscopic identification of trypomastigotes in fresh preparations of anticoagulated blood or buffy coat. Parasitemia decreases and is undetectable within 90 days of infection. Chronic T cruzi infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megaesophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of T cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis of chronic T cruzi infection relies on serologic detection of antibodies to this organism. However, no single serologic assay is sensitive and specific enough to be relied upon alone. Therefore, per current guidelines and the Centers for Disease Control and Prevention, serologic confirmation of chronic T cruzi infection requires positivity on 2 tests utilizing 2 different methodologies or 2 different T cruzi antigen preparations. When results are discordant, a testing by a third assay is recommended to resolve the initial results or, alternatively, repeat testing on a new sample may be required.

**Useful For:** Diagnosis of chronic Trypanosoma cruzi infection (Chagas disease) via lateral flow assay

**Interpretation:** Positive: Antibodies to Trypanosoma cruzi detected suggesting chronic T cruzi infection. Diagnosis of chronic T cruzi infection relies on the presence of appropriate exposure history and positive results by 2 distinct serologic assays. This patient was positive by both an anti-T cruzi IgG enzyme-linked immunosorbent assay (ELISA) using purified, extracted T cruzi antigens, and a lateral flow assay using recombinant T cruzi antigens.(1) Negative: No antibodies to T cruzi detected. Chronic T cruzi infection cannot be confirmed due to the discordant serologic results. Further testing (offered through the CDC) or repeat testing on a new sample is recommended.(1)
Reference Values:
Only orderable as a reflex. For more information see CHAG / Trypanosoma cruzi IgG Antibody ELISA, Serum.

Negative


TRYPN
70572

Trypsin Immunostain, Technical Component Only

Clinical Information: Trypsinogen is an enzyme involved in protein metabolism that is made by the acinar cells of the exocrine pancreas. After secretion into the small intestine, it is cleaved to its active form, trypsin. In normal pancreas, the antibody stains cells within acini. Ductal cells and islet cells are negative. The antibody to trypsin can be useful in classifying carcinomas of the pancreas by identifying cells with acinar differentiation. Carcinomas with ductal or endocrine differentiation will generally be negative.

Useful For: Identifying cells with acinar differentiation in the pancreas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


TRPTS
70573

Tryptase Immunostain, Technical Component Only

Clinical Information: In normal tissues, antibodies to tryptase stain mast cells with an intense cytoplasmic granular staining pattern. This marker has great utility in supporting a diagnosis of mast cell disease.

Useful For: A marker of mast cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TRYPA**

**Tryptase, Autopsy, Serum**

**Clinical Information:**
Tryptase, a neutral protease, is present within the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes. Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the protryptases reflect the total number of mass cells within the body, but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparin or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of beta-tryptase. After anaphylaxis, mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes. The levels decline under first-order kinetics with a half-life of approximately 2 hours. By comparison, histamine (another immunologic mediator released by activated mast cells) is cleared from blood within minutes. Increased serum levels may also occur after allergen challenge or in patients with systemic mastocytosis or mast cell activation syndrome.

**Useful For:**
Assessing autopsy cases for mast cell activation, which may occur as a result of anaphylaxis or allergen challenge Assessing patients with systemic mastocytosis or mast cell activation syndrome

**Interpretation:**
Increased concentrations of total tryptase may indicate mast cell activation occurring as a result of anaphylaxis or allergen challenge, or it may indicate an increased number of mast cells as seen in patients with mastocytosis. However, no specific cutoff value has been validated for autopsy specimens.

**Reference Values:**
No established reference values

**Clinical References:**

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**TRYPT**

**Tryptase, Serum**

**Clinical Information:**
Tryptase, a neutral protease, is a dominant protein component of the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes. Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the protryptases reflect the total number of mass cells within the body, but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparin or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of beta-tryptase. After anaphylaxis,
mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes. The levels decline under first-order kinetics with half-life of approximately 2 hours. By comparison, histamine (another immunologic mediator released by activated mast cells) is cleared from blood within minutes. Increased serum levels may also occur after allergen challenge or in patients with systemic mastocytosis or mast cell activation syndrome.

**Useful For:** Assessing mast cell activation, which may occur as a result of anaphylaxis or allergen challenge Assessing patients with systemic mastocytosis or mast cell activation syndrome

**Interpretation:** Levels of total tryptase in serum greater than or equal to 11.5 ng/mL may indicate mast cell activation occurring as a result of anaphylaxis or allergen challenge, or it may indicate increased number of mast cells as seen in patients with mastocytosis.

**Reference Values:**
<11.5 ng/mL


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**TRYPP**

**Tryptophan, Plasma**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism have been identified, including glutaric acidemia type 1, which affect other metabolic activities. Amino acid disorders can manifest at any time in a person's life, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Low plasma concentrations of tryptophan have been associated with clinical observations of insomnia, anxiety, and depression. Glutaric acidemia type 1 is an autosomal recessive disorder of tryptophan and lysine metabolism caused by a deficiency of glutaryl-CoA dehydrogenase. Early diagnosis and treatment is essential to help prevent encephalopathic crises leading to brain degeneration. These can be provoked by infections, trauma, fever, and fasting. Treatment consists of preventing neurodegeneration through L-carnitine supplementation and strict adherence to an emergency protocol. Dietary protein, in particular, lysine and tryptophan, is restricted during the vulnerable period of brain development from 0 to 5 years of age. In addition to other indices of malnutrition, the measurement of plasma concentration of tryptophan is used as an indicator of appropriate dietary therapy.

**Useful For:** Investigating inadequate tryptophan intake and monitoring dietary treatment

**Interpretation:** If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added including a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, if applicable.

**Reference Values:**
< or =23 months: 17-75 nmol/mL
2 years-17 years: 23-80 nmol/mL
> or =18 years: 29-77 nmol/mL

**Tryptophan, Random, Urine**

**Clinical Information:** Amino acids are the basic units that make up proteins and are crucial to virtually all metabolic processes in the body. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Hartnup disease is a rare, usually benign, autosomal recessive disorder of renal and intestinal neutral amino acid transport. Reduced intestinal absorption of tryptophan and subsequent loss in the urine lead to a reduction of available tryptophan for the synthesis of niacin. The clinical features associated with Hartnup disease include an erythematous skin rash on exposed surfaces that is identical to the rash seen in pellagra (niacin deficiency) and cerebral ataxia. Biochemically, it is characterized by increased renal excretion of tryptophan and other neutral amino acids. Newborn screening studies reveal that most affected individuals remain asymptomatic, suggesting that clinical expression of symptoms is dependent on additional genetic or environmental factors (ie, multifactorial disease).

**Useful For:** Aiding in the screening and monitoring of Hartnup disease

**Interpretation:** If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added, including a correlation to available clinical information and recommendations for additional biochemical testing, if applicable.

**Reference Values:**
- < or =35 months: 14-315 nmol/mg creatinine
- 3-8 years: 10-303 nmol/mg creatinine
- 9-17 years: 15-229 nmol/mg creatinine
- > or =18 years: 18-114 nmol/mg creatinine

**Clinical References:**

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**TTF41 (SPT24) + p40 Immunostain, Technical Component Only**

**Clinical Information:** Thyroid transcription factor 1 (TTF1) is a nuclear protein (detected by the chromogen 3,3'-diaminobenzidine: DAB) expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. The p40 antibody recognizes the deltaNp63 isoform of p63 (detected by the chromogen fast red). The predominant localization of p40 is in the basal layer of the stratified squamous and transitional epithelia. Given the relative specificity of TTF1 for cells of thyroid or lung origin, TTF1 is often included in a panel to identify the primary site for carcinomas of unknown origin. The p40 antibody may help to distinguish squamous cell carcinomas from other non-small cell carcinomas.

**Useful For:** Thyroid transcription factor 1 aids in the classification of carcinomas of unknown origin p40 aids in the classification of carcinomas and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.
Clinical References:


ATTRZ

TTR Gene, Full Gene Analysis, Varies

Clinical Information: The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. The most common hereditary amyloidosis is familial transthyretin amyloidosis; an autosomal dominant disorder caused by mutations in the transthyretin (TTR) gene. The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic TTR protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Typically, TTR-associated amyloidosis is progressive over a course of 5 to 15 years and the most common cause of death is cardiomyopathy. Affected individuals may present with a variety of symptoms, including peripheral neuropathy, blindness, cardiomyopathy, nephropathy, autonomic nervous dysfunction, or bowel dysfunction. More than 90 mutations have now been identified within the TTR gene, which cause TTR-associated familial amyloidosis. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of amyloidosis. However, several different mutations have been identified which exhibit considerable clinical overlap. It is important to note that this assay does not detect mutations associated with non-TTR forms of familial amyloidosis. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

Useful For: Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:


RTRP2

Tubular Reabsorption of Phosphorus, Random Urine and Serum

Current as of June 14, 2021 12:13 pm CDT

800-533-1710 or 507-266-5700 or mayocliniclabs.com

Page 2526
Clinical Information: The tubular reabsorption of phosphate (TRP) is the fraction (or percent) of filtered phosphorus that is reabsorbed by renal tubules. Its measurement is useful when evaluating patients with hypophosphatemia. In general, a reduced TRP in the presence of hypophosphatemia is indicative of a renal defect in phosphate reabsorption. The ratio of the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate (TmP/GFR) is considered the most convenient way to evaluate renal phosphate transport and is referred to as the theoretical renal phosphate threshold. This corresponds to the theoretical lower limit of plasma phosphate below which all filtered phosphate would be reabsorbed. Although direct measurements of parathyroid hormone, which increases renal phosphate excretion, have replaced much of the utility of TmP/GFR measurements, it may still be useful in assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia.

Useful For: Assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia including hypophosphatemic rickets, tumor-induced osteomalacia, and tumoral calcinosis. Adjusting phosphate replacement therapy in severe deficiency states monitoring the renal tubular recovery from acquired Fanconi syndrome.

Interpretation: Interpretation of tubular reabsorption of phosphate (TRP) and the maximum rate of TRP to the glomerular filtration rate (TmP/GFR) is dependent upon the clinical situation and should be interpreted in conjunction with the serum phosphorous concentration. TmP/GFR is independent of dietary phosphorus intake, tissue release of phosphorus, and GFR.

Reference Values:
TUBULAR REABSORPTION OF PHOSPHORUS
>80%
(Although, tubular reabsorption of phosphorus levels must be interpreted in light of the prevailing plasma phosphorus and glomerular filtration rate.)

TUBULAR MAXIMUM PHOSPHORUS REABSORPTION/GLOMERULAR FILTRATION RATE (TmP/GFR)
2.6-4.4 mg/dL (0.80-1.35 mmol/L)

PHOSPHORUS (INORGANIC)
Males
1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are <12 months of age.
Females
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are <12 months of age.

PHOSPHORUS, Random Urine
No established reference values

Random urine phosphorus may be interpreted in conjunction with serum phosphorus, using both values to calculate fractional excretion of phosphorus.

The calculation for fractional excretion (FE) of phosphorus (P) is
FE(P)= ([P(urine)XCreat(serum)]/[P(serum)XCreat(urine)]) X 100

CREATININE Serum
Males(1)
0-11 months: 0.17-0.42 mg/dL  
1-5 years: 0.19-0.49 mg/dL  
6-10 years: 0.26-0.61 mg/dL  
11-14 years: 0.35-0.86 mg/dL  
> or =15 years: 0.74-1.35 mg/dL  

Females(1)  
0-11 months: 0.17-0.42 mg/dL  
1-5 years: 0.19-0.49 mg/dL  
6-10 years: 0.26-0.61 mg/dL  
11-15 years: 0.35-0.86 mg/dL  
> or =16 years: 0.59-1.04 mg/dL  

CREATININE, Random Urine  
16-326 mg/dL  
Reference values have not been established for patients who are less than 18 years of age.

**Clinical References:**  

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**Tumor Necrosis Factor (TNF), Plasma**

**Clinical Information:** Tumor necrosis factor (TNF)-alpha is expressed primarily by activated monocytes as part of the innate immune response to various microbes, gram-negative bacteria in particular. (1) TNF-alpha is synthesized as a type II membrane protein, which can be cleaved by a membrane-associated metalloproteinase. The subunit that is released will polymerize to form a homotrimer, which is the circulating form of TNF-alpha. The primary function of TNF-alpha is to recruit other leukocytes to the site of infection and to stimulate their activation. TNF-alpha also has some systemic effects, including induction of fever through action on the hypothalamus. In cases of severe gram-negative bacterial infection, septic shock can occur. Septic shock is induced by large-scale production of inflammatory cytokines, including TNF-alpha. This disorder is characterized by hypotension, disseminated intravascular coagulation, tachycardia, and increased respiration, and can be fatal. Dysregulation of TNF-alpha expression is thought to be a critical pathogenic mechanism in numerous autoimmune diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). (2) There are currently 5 monoclonal antibodies approved by the FDA for blockage of TNF-alpha as a clinical treatment. (3, 4) The different drugs are approved for various diseases, with some available for treatment of pediatric IBD and juvenile RA.

**Useful For:** Evaluation of patients with suspected systemic infection, in particular infection caused by gram-negative bacteria Evaluation of patients with suspected chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, or ankylosing spondylitis

**Reference Values:**  
< or =2.8 pg/mL

**Clinical References:**  
1. Clark IA: How TNF was recognized as a key mechanism of disease. Cytokine Growth Factor Rev 2007;18:335-343  
**Tuna, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to tuna Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Turkey Feathers, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and...
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to turkey feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


**FGORG 57641 Turkey IgG Interpretation:**

**Reference Values:**

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**TURK 82702 Turkey, IgE, Serum Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to turkey
Defining the allergen responsible for eliciting signs and symptoms
Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode
-To confirm sensitization prior to beginning immunotherapy
-To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
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<tr>
<td>0</td>
<td>&lt;0.35</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;99.99</td>
<td>Very Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Turmeric (Curcuma longa) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**Tyrophagus putrescentiae, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing a diagnosis of an allergy to Tyrophagus putrescentiae. Defining the allergen responsible for eliciting signs and symptoms. Identifying allergens responsible for allergic disease and/or anaphylactic episode. To confirm sensitization prior to beginning immunotherapy. To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Tyrosinase (TYROS) Immunostain, Technical Component Only**

**Clinical Information:** Tyrosinase is expressed in the majority of melanomas, making it a useful diagnostic marker. This antibody will detect the tyrosinase enzyme in the cytoplasm of normal melanocytes as well as cells of malignant melanoma.

**Useful For:** Aids in the identification of normal melanocytes and malignant melanoma.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**TYRGP 608033 Tyrosine Disorders Gene Panel, Varies**

**Clinical Information:** Tyrosinemia type 1 (hepatorenal tyrosinemia: HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) in the tyrosine degradation pathway. HT-1 primarily affects the liver, kidneys, and peripheral nerves causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma (HCC). The incidence of HT-1 is approximately 1 in 100,000 live births. Other causes for increased levels of tyrosine in plasma amino acid analysis include tyrosinemia type II, tyrosinemia type III, and hawkinsinuria, although diagnosis for this condition is typically based on the presence of hawkinsin in the urine. Alkaptonuria, another condition in the tyrosine degradation pathway, is characterized by increased plasma and urinary homogentisic acid. Urine turns dark upon standing and alkalinization.

**Useful For:** Follow up for abnormal biochemical results suggestive of a tyrosine disorder
Identifying variants within genes known to be associated with tyrosine disorders, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**TYRBS 607550 Tyrosinemia Follow Up Panel, Blood Spot**

**Clinical Information:** Tyrosinemia type 1 (Hepatorenal Tyrosinemia, HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). HT-1 primarily affects the liver, kidneys, and peripheral nerves causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma (HCC). The incidence of HT-1 is approximately 1 in 100,000 live births. Affected individuals can show a partial response to dietary restriction of phenylalanine and tyrosine, but dietary treatment in conjunction with the administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC; nitisinone), an inhibitor of the proximal tyrosinemia pathway, is very effective when initiated in newborns. Outcome data are promising and to date, newborn patients treated with NTBC have not developed acute liver disease, neurologic crises, or HCC. According to treatment guidelines established in 2017, monitoring of blood NTBC concentration and succinylacetone (SUAC) levels along with measuring the dietary intake of amino acids, including tyrosine and phenylalanine are part of an individualized surveillance plan for patients with HT-1. (1) Monthly analysis of SUAC, NTBC concentration, and amino acids is suggested for the first year of life with the same compounds being monitored every 3 months to age 5 years and every 6 months thereafter. The analytes encompassed in this assay satisfy the recommendations for...
diagnosis and monitoring of HT-1. In particular, for NTBC, the current guidelines recommend 40 nmol/mL to 60 nmol/mL plasma concentration, which corresponds to a target range for NTBC in dried blood spots of 17 nmol/mL to 26 nmol/mL based on a blood to plasma conversion factor of 2.34. Data from the validation of this assay suggests that NTBC dosing could be individualized while not to exceed DBS levels of 26 nmol/mL.(3)

**Useful For:** Monitoring of individuals with tyrosinemia type I (HT-1) Diagnosis of HT-1 along with urine organic acids (OAU), liver function tests, alpha-fetoprotein, and molecular genetic analysis of the fumarylacetoacetate hydrolase (FAH) gene

**Interpretation:** Quantitative results with reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information.

**Reference Values:**

**TYROSINE:**
<4 weeks 40.0-280.0 nmol/mL
> or =4 weeks 25.0-150.0 nmol/mL

**PHENYLALANINE:**
27.0-107.0 nmol/mL

**METHIONINE:**
11.0-45.0 nmol/mL

**SUCCINYLACETONE:**
<1.00 nmol/mL

**NITISINONE:**
<0.7 nmol/mL

**Clinical References:**

**TYRSC 610495 Tyrosinemia Follow-Up Panel, Self-Collect, Blood Spot**

**Clinical Information:** Tyrosinemia type 1 (hepatoportal tyrosinemia: HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetacetate hydrolase. HT-1 primarily affects the liver, kidneys, and peripheral nerves causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma (HCC). The incidence of HT-1 is approximately 1 in 100,000 live births. Affected individuals can show a partial response to dietary restriction of phenylalanine and tyrosine, but dietary treatment in conjunction with the administration of 2-((2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC; nitisinone), an inhibitor of the proximal tyrosinemia pathway, is very effective when initiated in newborns. Outcome data are promising and to date, newborn patients treated with NTBC have not developed acute liver disease, neurologic crises, or HCC. According to treatment guidelines established in 2017, monitoring of blood NTBC...
concentration and succinylacetone (SUAC) levels along with measuring the dietary intake of amino acids, including tyrosine and phenylalanine are part of an individualized surveillance plan for patients with HT-1.(1) Monthly analysis of SUAC, NTBC concentration, and amino acids is suggested for the first year of life with the same compounds being monitored every 3 months to age 5 years and every 6 months thereafter. The analytes encompassed in this assay satisfy the recommendations for diagnosis and monitoring of HT-1. In particular, for NTBC, the current guidelines recommend 40 nmol/mL to 60 nmol/mL plasma concentration, which corresponds to a target range for NTBC in dried blood spots of 17 nmol/mL to 26 nmol/mL based on a blood to plasma conversion factor of 2.34.(2) Data from the validation of this assay suggests that NTBC dosing could be individualized while not to exceed DBS levels of 26 nmol/mL.(3)

**Useful For:** Monitoring of individuals with tyrosinemia type I (hepatorenal tyrosinemia)

**Interpretation:** Quantitative results with reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information.

**Reference Values:**

**TYROSINE**
- <4 weeks: 40.0-280.0 nmol/mL
- > or =4 weeks: 25.0-150.0 nmol/mL

**PHENYLALANINE:**
- 27.0-107.0 nmol/mL

**METHIONINE:**
- 11.0-45.0 nmol/mL

**SUCCINYLACETONE:**
- <1.00 nmol/mL

**NITISINONE:**
- <0.7 nmol/mL

**Clinical References:**

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**FSABI 58004**

**Tysabri (Natalizumab) Immunogenicity**

**Reference Values:**
Negative

**UBE3Z 35565**

**UBE3A Gene, Full Gene Analysis, Varies**

**Clinical Information:** Angelman syndrome (AS) is characterized by significant developmental delay and mental retardation, ataxia, jerky arm movements, unprovoked laughter, seizures, and virtual...
absence of speech. AS has several known genetic causes. About 65% to 80% of affected individuals have a de novo deletion of essentially the same region of chromosome 15 detected for Prader-Willi syndrome (PWS): 15q11.2-13. The deletion can often be identified by high-resolution chromosome analysis in conjunction with FISH analysis. Molecular testing has shown that the AS deletion occurs only on the copy of chromosome 15 inherited from the mother. In about 5% of patients with AS, the affected individuals have inherited 2 copies of chromosome 15 from their father (paternal uniparental disomy) and no copies of chromosome 15 from their mother. Thus, the individuals with AS resulting from deletion or uniparental disomy are deficient for maternally derived genes from chromosomes 15. Deletions and uniparental disomy occur as de novo events during conception, so the recurrence risk to siblings is very low. Both of these genetic alterations, along with imprinting center defects (accounting for another 2%-5% of AS cases), cause an abnormal methylation pattern in the PWS/AS region of chromosome 15. Another 10% of patients with AS have a documented mutation in the UBE3A gene located in the PW/AS region on chromosome 15. Mutations can either be maternally inherited in an autosomal dominant fashion or de novo. If the mutation is inherited, the risk to all future pregnancies is 50%. If testing of the affected individual's mother confirms she does not carry the mutation, the risk to future pregnancies is low but not zero, as cases of germline mosaicism have been reported. Individuals with a UBE3A mutation will display a normal methylation pattern. No chromosomal or DNA abnormality has been identified in the remainder of clinically diagnosed AS patients (15%-25%). These patients may have genetic alterations that cannot be detected by current testing methods or alterations in as yet unidentified genes. Initial studies to rule-out AS should include high-resolution cytogenetic analysis (CMS / Chromosome Analysis, for Congenital Disorders, Blood) to identify chromosome abnormalities that may have phenotypic overlap with AS, and methylation-sensitive, multiple ligation-dependent probe amplification (PWAS / Prader-Willi/Angelman Syndrome, Molecular Analysis) to identify deletions, duplications, and methylation defects. In cases where methylation analysis is negative, sequencing of the UBE3A gene may provide additional diagnostic information.

**Useful For:** Confirmation of a diagnosis of Angelman syndrome in patients who have previously tested negative by methylation analysis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**UBIQ 70578**

**Ubiquitin (UBIQ) Immunostain, Technical Component Only**

**Clinical Information:** Ubiquitin is a polypeptide of approximately 8.5 kD found in filamentous inclusions and cytosome-related organelles in human idiopathic neurodegenerative diseases, including Alzheimer disease, Pick disease, Lewy body dementia, and Parkinson disease. Ubiquitin is also expressed in Rosenthal fibers in astrocytomas. Ubiquitin protein complexes have also been found in primary lysosome-related granules in mature neutrophils. Ubiquitin labels the periphery of senile plaques and of neurofibrillary tangles in Alzheimer disease, Lewy bodies in Parkinson disease, and Mallory bodies in alcoholic liver disease.

**Useful For:** Classification of neurodegenerative diseases

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation
is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**UDP-Galactose 4' Epimerase, Blood**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared to intermediate epimerase deficiency galactosemia which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and renal dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of renal and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, females with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6700 in African American infants to 1 in 70,000 infants of European ancestry. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency. The quantitative measurement of Gal-1-P (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Newborn screening varies from state to state and identifies potentially affected individuals by measuring total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are normal, but an infant has an elevated Gal-1-P, then epimerase deficiency galactosemia is to be considered. Molecular testing via sequencing of the GALE gene may be performed. See Galactosemia Testing Algorithm in Special Instructions.
Useful For: Diagnosis of UDP-galactose 4’ epimerase deficiency

Interpretation: An interpretive report will be provided.

Reference Values:
> or = 3.5 nmol/h/mg of hemoglobin


**UGTFG**

**UDP-Glucuronosyl Transferase 1A1 (UGT1A1), Full Gene Sequencing, Varies**

**Clinical Information:** The UGT1A1 gene is part of a gene complex located on chromosome 2 that encodes several enzymes called uridine diphosphate (UDP)-glucuronosyl transferases. These enzymes perform a chemical reaction called glucuronidation, a major pathway that enhances the elimination of small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble metabolites that can be excreted from the body. The UGT1A1 enzyme, primarily found in the liver, is responsible for the glucuronidation of bilirubin, converting it from the toxic form of bilirubin (unconjugated bilirubin) to its nontoxic, water-soluble form (conjugated bilirubin). Genetic variants in UGT1A1 may cause reduced or absent UGT1A1 enzymatic activity, resulting in conditions associated with unconjugated hyperbilirubinemia including Gilbert syndrome and Crigler-Najjar syndromes types I and II. Gilbert syndrome is the most common hereditary cause of increased bilirubin and is characterized by total serum bilirubin levels of 1 to 6 mg/dL. Gilbert syndrome is generally considered to be an autosomal recessive disorder, although autosomal dominant inheritance has been suggested in some cases.(1) Gilbert syndrome is caused by a 25% to 50% reduction in glucuronidation activity of the UGT1A1 enzyme and is characterized by episodes of mild intermittent jaundice and the absence of liver disease. Crigler-Najjar syndromes types I and II (CN1 and CN2) are autosomal recessive disorders caused by more severe reductions in UGT1A1 glucuronidation activity. CN1 is the most severe form, with complete absence of enzyme activity and total serum bilirubin levels of 20 to 45 mg/dL. Infants with CN1 present with jaundice shortly after birth that persists thereafter.(2) CN2 is milder than CN1, with at least partial UGT1A1 activity and total serum bilirubin ranging from 6 to 20 mg/dL. Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN2; CN1 does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause bilirubin-induced brain damage, known as kernicterus. In addition to phenobarbital, treatments of CN may include: phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation. In addition to the role of UGT1A1 in bilirubin metabolism, this enzyme also plays a role in the metabolism of several drugs. UGT1A1 is involved in the metabolism of irinotecan, a topoisomerase I inhibitor. Irinotecan is a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. It is a prodrug that forms an active metabolite, SN-38. SN-38 is normally inactivated by conjugation with glucuronic acid followed by biliary excretion into the gastrointestinal tract. If UGT1A1 activity is impaired or deficient, SN-38 fails to become conjugated with glucuronic acid, increasing the concentration of SN-38. This can result in severe neutropenia. The combination of neutropenia with diarrhea can be life-threatening.(3,4) Additional drugs have also been associated with an increased risk for adverse outcomes in patients with reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 variants associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice). The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. In this assay, the promoter, exons, and exon-intron boundaries
are assessed for variants. (5)

**Useful For:** Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1, including irinotecan, atazanavir, nilotinib, pazopanib, and belinostat. Identifying individuals who are at risk of hyperbilirubinemia. Follow-up testing for individuals with a suspected UGT1A1 variant, who had negative TA repeat region testing. Establishing a diagnosis of Gilbert, Crigler-Najjar syndrome type I or type II. Establishing carrier status for Gilbert, Crigler-Najjar syndrome type I or type II.

**Interpretation:** An interpretive report will be provided that includes assessment of risk for UGT1A1-associated adverse drug reactions as well as interpretation for hyperbilirubinemia syndromes. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Clinical Information:** Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP)-glycuronosyl transferase 1A1 (UGT1A1), is responsible for phase II conjugation of certain drugs, like atazanavir, irinotecan, nilotinib, pazopanib, and belinostat. UGT1A1 is additionally responsible for glucuronide conjugation of bilirubin, which renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. Reduced UGT1A1 gene transcription due to variation in the number of thymine-adenine (TA) repeats in the TATA box of the gene promoter and c.211G>A (*6) results in reduced enzymatic activity and an increased risk for adverse outcomes in response to drugs metabolized by UGT1A1. These variants are also associated with Gilbert syndrome (unconjugated hyperbilirubinemia). The TA repeat number may vary from 5 to 8 TA (TA5-TA8) repeats, with 6 TA (TA6) repeats being the most common allele. TA6 is the reference allele and is considered to have normal UGT1A1 expression. In addition, the rare TA5 repeat (*36: c.-41_-40delTA) has normal UGT1A1 expression. Individuals with TA7 repeat (*28: c.-41_-40dupTA) or the rare TA8 repeat (TA8 or *37: c.-43_-40dupTATA, not distinguished from TA7...
with this assay) have decreased expression of UGT1A1. Approximately 10% to 15% of white and African American populations are homozygous for the TA7 repeat (*28/*28). UGT1A1 is involved in the metabolism of irinotecan, a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. If UGT1A1 activity is reduced or deficient, the active irinotecan metabolite (SN-38) is less efficiently conjugated with glucuronic acid, which leads to an increased concentration of SN-38. This in turn can result in severe neutropenia; and the combination of neutropenia with diarrhea can be life-threatening. Individuals who are homozygous for *28 (TA7) have a 50% higher risk of experiencing severe (grade 4 or 5) neutropenia following the administration of irinotecan. Approximately 40% of individuals treated with irinotecan are heterozygous for the TA7 repeat allele (ie, TA6/TA7 or heterozygous *28). These individuals are also at increased risk of grade 4 neutropenia. The drug label for irinotecan indicates that individuals homozygous or heterozygous for TA repeat variants have a higher risk for severe or life-threatening neutropenia. The risk is thought to be greatest in individuals who receive irinotecan once every 3 weeks. Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The FDA drug labels for atazanavir, nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have reduced activity alleles. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment that indicate patients who are homozygous for a reduced activity (decreased expression) allele should be considered for an alternate medication due to the significant risk for developing hyperbilirubinemia (jaundice).(2) Gilbert syndrome (GS), found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with usually benign, mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Homozygosity for the reduced activity alleles, UGT1A1*6 (c.211G>A) allele, TA7, and TA8, or compound heterozygosity (*6, TA7, or TA8) is consistent with a diagnosis of Gilbert syndrome. Heterozygosity for *6, TA7 or TA8 is consistent with carrier status for Gilbert syndrome.

**Useful For:** Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1; especially irinotecan but also atazanavir, nilotinib, pazopanib, and belinostat. Identifying individuals with Gilbert syndrome due to the presence of homozygous UGT1A1*6 (c.211G>A, based on NM_000463.2) allele, TA7, homozygous TA8, or compound heterozygous *6, TA7 or TA8. Identifying individuals who are carriers of Gilbert syndrome due to the presence of heterozygous TA7 or TA8.

**Interpretation:** An interpretive report will be provided. Drug-drug interactions must be considered when predicting the UGT1A1 phenotype, especially in individuals heterozygous for the TA7 polymorphism. For additional information regarding pharmacogenic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Ulocladium chartarum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Ulocladium chartarum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Uniparental Disomy, Varies

Clinical Information: Uniparental disomy (UPD) occurs when a child inherits 2 copies of a chromosome from 1 parent and no copies of that chromosome from the other parent. This error in division occurs during the formation of egg or sperm cells (meiosis). When an error causing UPD occurs during meiosis I both chromosome homologs from a single parent are transmitted, and heterodisomy results. When the error causing UPD occurs during meiosis II or as a postzygotic event, and a single parental homolog is transmitted to offspring in duplicate, isodisomy results. Meiotic recombination events within the context of UPD often result in a mixture of heterodisomy and
isodisomy. UPD can involve an entire chromosome or only a segment. Mosaicism for UPD also occurs in combination with either chromosomally normal or abnormal cell lines. When UPD occurs, the imbalance of maternal versus paternal genetic information for the involved chromosome can be associated with clinical symptoms in the affected child. UPD does not always impart an abnormal clinical phenotype however. In fact, while isodisomy can result in disease due to a recessive allele at any location, heterodisomy is not expected to result in an abnormal clinical phenotype unless the involved chromosome or chromosomal segment includes imprinted genes. Imprinted genes demonstrate differential expression depending on parent of origin. Disorders that result from UPD of imprinted genes are not due to a defect in the imprinting mechanism itself, but rather they are due to an unbalanced parental contribution of normally imprinted alleles that results in altered expression of imprinted genes. For example, when maternal UPD 15 occurs (2 copies of the maternal chromosome 15 instead of 1 maternal and 1 paternal copy of chromosome 15), it causes Prader-Willi syndrome due to the lack of paternally expressed genes at the imprinted site. UPD has been described for many but not all chromosomes. In addition to the rare cases of autosomal recessive disease that result from isodisomy, clinical syndromes associated with UPD have been described for only a few chromosomes, including Russell-Silver syndrome (UPD 7), Prader-Willi syndrome (UPD 15), Angelman syndrome (UPD 15), transient neonatal diabetes (UPD 6), and UPD of chromosome 14. UPD cannot be identified by gross cytogenetic analysis and requires DNA-based analysis using multiple polymorphic markers spanning the chromosome of interest. Specimens from both parents and the child or fetus are required.

**Useful For:** Evaluation of patients presenting with mosaicism, confined placental mosaicism, or Robertsonian translocations Evaluation of patients presenting with features of disorders known to be associated with uniparental disomy (eg, Russell-Silver syndrome) Evaluation of disease mechanism in individuals with rare autosomal recessive disease and only one carrier parent

**Reference Values:** An interpretative report will be provided.

**Clinical References:**

**FURA 90316**

**Uranium, Urine**

**Interpretation:** Specimens for elemental testing should be collected in certified metal-free containers. Elevated results for elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen.

**Reference Values:**
Reporting limit determined each analysis

Normally: Less than 0.1 mcg/L

**UCDP 608020**

**Urea Cycle Disorders Gene Panel, Varies**

**Clinical Information:** Urea cycle disorders (UCD) are a group of inherited disorders of nitrogen detoxification that result when any of the enzymes in the urea cycle have reduced or absent activity. These disorders include carbamoylphosphate synthetase I (CPS I) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinate synthetase deficiency (citrullinemia), argininosuccinic acid lyase deficiency (argininosuccinic aciduria), arginase deficiency, the cofactor producer, N-acetyl glutamate...
synthetase (NAGS) deficiency, and two amino acid transporters, ornithine translocase deficiency (hyperornithinemia, hyperammonemia, homocitrullinuria syndrome: HHH syndrome) and citrin deficiency. The role of the urea cycle is to metabolize and clear waste nitrogen, and defects in any of the steps of the pathway can result in an accumulation of toxic ammonia in the nervous system. The urea cycle is also responsible for endogenous production of the amino acids citrulline, ornithine, and arginine. Infants with a complete urea cycle enzyme deficiency typically appear normal at birth, but they present in the neonatal period with lethargy, seizures, hyper- or hypoventilation, and ultimately coma or death, as a result of elevated ammonia levels. Individuals with partial enzyme deficiency may present later in life, typically following an acute illness or other catabolic stressor. Symptoms may be less severe and may appear as episodes of psychosis, lethargy, cyclical vomiting, and behavioral abnormalities. Patients with impaired ornithine metabolism due to ornithine aminotransferase (OAT) deficiency may present with childhood onset myopia progressing to vision loss in the 4th to 6th decades of life. Patients may or may not have accompanying hyperammonemia, but display marked elevations in plasma ornithine. All of the UCD are inherited as autosomal recessive disorders, with the exception of OTC deficiency, which is X-linked. UCD may be suspected with elevated ammonia, normal anion gap, and a normal glucose. This comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features given the broad clinical spectrum and genetic heterogeneity of UCD. Molecular genetic testing can help to distinguish among the conditions and allows for diagnostic confirmation. A combination of biochemical tests including quantitative plasma amino acids (AAQP/ Amino Acids, Quantitative, Plasma) and urinary orotic acid (OROT/ Orotic Acid, Random, Urine) are recommended as the first-tier test to assess patients for UCD. Acute treatment for UCD consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been used with success in treating some patients.

**Useful For:** Follow up for abnormal biochemical results suggestive of a urea cycle disorder (UCD) Establishing a molecular diagnosis for patients with a UCD Identifying variants within genes known to be associated with UCD, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Clinical Information:** Byproducts of nitrogen metabolism are present in high concentration in urine compared to blood and serve as a surrogate marker for the identification of urine leakage into a body compartment. Concentrations of creatinine or urea nitrogen that exceed the concentration found in a concurrent sample of blood are suggestive of the presence of urine. (1) Peritoneal, abdominal, pelvic drain fluids: Disruption of the urinary tract with subsequent leakage of urine into body cavities may be considered as part of the differential diagnosis when body fluid effusions develop of unknown origin. (2) Metabolites such as creatinine or urea that are contained in urine at high concentrations are good candidates to measure in body fluids for this investigation. Elevated concentrations may elicit a more focused radiologic examination to identify possible bladder rupture or perforation or the development of urinary fistula, which are typically corrected by surgical intervention. Peritoneal dialysis fluid: Peritoneal dialysis (PD) is a type of dialysis in which hyperosmotic fluid is passed into the patient's peritoneal cavity for a prescribed dwell time, wherein the peritoneum is employed as the dialysis membrane. The dwell fluid containing waste molecules removed by dialysis is drained and replaced with fresh fluid and the process repeated. Measurements of urea, creatinine, glucose, or other electrolytes in serum, urine, and the peritoneal dialysate fluid, aid in the assessment of peritoneal membrane transport characteristics and serve as markers of dialysis adequacy. Adequacy of PD is important to monitor because patients who maintain a sufficient clearance over time have longer survival. (2) Peritoneal urea clearance volume of distribution or urea (Kt/V) is calculated to measure solute clearance from the daily peritoneal urea clearance (Kt), and the volume of distribution of urea (V). Adequacy and membrane transport characteristics are calculated by plugging in the appropriate laboratory parameters into software packages used by dialysis centers.

**Useful For:** Identifying the presence of urine as a cause for accumulation of fluid in a body compartment Assessing adequacy of peritoneal dialysis treatment protocols

**Interpretation:** Peritoneal and drain fluid concentrations should be compared to serum or plasma. A fluid to serum ratio of greater than 1.0 suggests the specimen may be contaminated with urine. (1) Peritoneal dialysate urea nitrogen concentrations can be used to calculate the adequacy of peritoneal dialysis by monitoring solute clearance over time. (3) All other fluids: Results should be interpreted in conjunction with serum urea nitrogen and other clinical findings.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Urea, 24 Hour, Urine**

**Clinical Information:** Urea is a low molecular weight substance (60 Da) that is freely filtered by glomeruli, and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors that tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors that reduce urea excretion include low protein intake and conditions that result in low urine output (eg, dehydration).

**Useful For:** Assessment of protein intake and/or nitrogen balance

**Interpretation:** Because multiple factors (glomerular filtration rate, dietary protein intake, protein catabolic rate, hydration state, etc.) can independently affect the urinary excretion of urea, all of these factors must be taken into account when interpreting the results.

**Reference Values:**
> or =18 years: 7-42 g/24 hours
Reference values have not been established for patients who are less than 18 years of age.

**Clinical References:**

**URCON 614061**

**Urea, Random, Urine**

**Clinical Information:** Urea is a low molecular weight substance (60 Da) that is freely filtered by glomeruli, and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end-product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors that tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors that reduce urea excretion include low protein intake and conditions that result in low urine output (eg, dehydration). Urea excretion is a useful marker of protein metabolism. In oliguric patients with a rising creatinine a fractional excretion of urea below 35% is consistent with a prerenal cause, while values above 35% are more consistent with acute kidney injury. The fractional excretion of sodium is also used for this purpose but may be more affected by diuretics. Therefore, the fractional excretion of urea may be particularly useful for patients receiving diuretics.

**Useful For:** Assessment of kidney failure (prerenal vs acute kidney injury)

**Interpretation:** Fractional excretion of urea under 35% is consistent with a prerenal cause.

**Reference Values:**
No established reference values

Random urine urea may be interpreted in conjunction with serum urea, using both values to calculate fractional excretion of urea.

The calculation for fractional excretion (FE) of urea is

FE(U)= ([U(urine)XCreat(serum)]/[U(serum)XCreat(urine)]) X 100

**Clinical References:**

**URBRP 65133**

**Ureaplasma species, Molecular Detection, PCR, Blood**

**Clinical Information:** Ureaplasma urealyticum and U parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and they have been associated with infected renal stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningoecephalitis and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients. In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species
is laborious, requiring a high degree of technical skill and taking several days. PCR detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

**Useful For:** Rapid, sensitive, and specific identification of Ureaplasma urealyticum and U parvum from whole blood

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and U parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**Ureaplasma species, Molecular Detection, PCR, Plasma**

**Clinical Information:** Ureaplasma urealyticum and U parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and they have been associated with infected renal stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningocencephalitis and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients.(1) In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. PCR detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

**Useful For:** Rapid, sensitive, and specific identification of Ureaplasma urealyticum and U parvum from plasma

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and U parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U
Ureaplasma species, Molecular Detection, PCR, Varies

Clinical Information: Ureaplasma urealyticum and Ureaplasma parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and have been associated with infected renal stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningoencephalitis and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients. In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. Polymerase chain reaction (PCR) detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. The PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and U parvum from genitourinary, reproductive, bone, spine and joint, and lower respiratory sources This test is not intended for medicolegal use

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Ureaplasma urealyticum and Ureaplasma parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but it does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities less than the limit of detection of the assay.

Reference Values: Not applicable

Uric Acid, 24 Hour, Urine

**Clinical Information:** Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and endogenous nucleic acid breakdown.

**Useful For:** Assessment and management of patients with kidney stones, particularly uric acid stones

**Interpretation:** Urinary uric acid excretion is elevated in a significant proportion of patients with uric acid stones. Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins.

**Reference Values:**
- Males ≥ 18 years old: 200-1,000 mg/24 hours
- Females ≥ 18 years old: 250-750 mg/24 hours

Reference values have not been established for patients who are less than 18 years of age. The reference value is for a 24-hour collection.

**Clinical References:**

Uric Acid, Body Fluid

**Reference Values:**
- Units: mg/dL

Uric Acid, Serum

**Clinical Information:** Uric acid is the final product of purine metabolism in humans. Purines, compounds that are vital components of nucleic acids and coenzymes, may be synthesized in the body or they may be obtained by ingesting foods rich in nucleic material (e.g., liver, sweetbreads). Approximately 75% of the uric acid excreted is lost in the urine; most of the remainder is secreted into the gastrointestinal tract where it is degraded to allantoin and other compounds by bacterial enzymes. Asymptomatic hyperuricemia is frequently detected through biochemical screening. The major causes of hyperuricemia are increased purine synthesis, inherited metabolic disorder, excess dietary purine intake, increased nucleic acid turnover, malignancy, cytotoxic drugs, and decreased excretion due to chronic renal failure or increased renal reabsorption. Long-term follow-up of these patients is undertaken because many are at risk of developing renal disease; few of these patients ever develop the clinical syndrome of gout. Hypouricemia, often defined as serum urate below 2.0 mg/dL, is much less common than hyperuricemia. It may be secondary to severe hepatocellular disease with reduced purine synthesis, defective renal tubular reabsorption, overtreatment of hyperuricemia with allopurinol, as well as some cancer therapies (e.g., 6-mercaptopurine).

**Useful For:** Diagnosis and treatment of renal failure Monitoring patients receiving cytotoxic drugs and a variety of other disorders, including gout, leukemia, psoriasis, starvation and other wasting conditions
**Interpretation:** Hyperuricemia is most commonly defined by serum or plasma uric acid concentrations above 8.0 mg/dL in males or above 6.1 mg/dL in females.

**Reference Values:**

**Males**
- 1-10 years: 2.4-5.4 mg/dL
- 11 years: 2.7-5.9 mg/dL
- 12 years: 3.1-6.4 mg/dL
- 13 years: 3.4-6.9 mg/dL
- 14 years: 3.7-7.4 mg/dL
- 15 years: 4.0-7.8 mg/dL
- > or =16 years: 3.7-8.0 mg/dL

Reference values have not been established for patients who are <12 months of age.

**Females**
- 1 year: 2.1-4.9 mg/dL
- 2 years: 2.1-5.0 mg/dL
- 3 years: 2.2-5.1 mg/dL
- 4 years: 2.3-5.2 mg/dL
- 5 years: 2.3-5.3 mg/dL
- 6 years: 2.3-5.4 mg/dL
- 7-8 years: 2.3-5.5 mg/dL
- 9-10 years: 2.3-5.7 mg/dL
- 11 years: 2.3-5.8 mg/dL
- 12 years: 2.3-5.9 mg/dL
- > or =13 years: 2.7-6.1 mg/dL

Reference values have not been established for patients who are <12 months of age.


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**RURC1 614048**

**Uric Acid/Creatinine Ratio, Random, Urine**

**Clinical Information:** Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and endogenous nucleic acid breakdown. Acute uric acid nephropathy can cause acute renal failure due to uric acid precipitation within tubules. This is most commonly seen in patients with hematologic malignancies (eg, lymphoma, leukemia), often after acute lysis of cells by chemotherapy. Less commonly this may be seen with seizures, treatment of solid tumors, overproduction of uric acid in metabolic disorders such as Lesch-Nyhan syndrome or decreased uric acid reabsorption in the proximal nephron due to tubular disorder (Fanconi syndrome).

**Useful For:** Differentiation of acute uric acid nephropathy from other causes of acute kidney failure

For patients who cannot collect a 24-hour specimen, typically small children, a uric acid to creatinine ratio can be used to approximate 24-hour excretion

**Interpretation:** Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins. A uric acid to creatinine ratio (mg/mg) greater than 1.0 is consistent with acute uric acid nephropathy, whereas values less than 0.75 are consistent with other causes of acute renal failure.(1) A timed 24-hour collection is usually the preferred method for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of clinical use in 2 scenarios, however: -When acute renal failure secondary to uric acid is suspected, a uric acid to creatinine ratio (mg/mg) greater than 1.0 is consistent with acute uric acid nephropathy, whereas values less than 0.75 are consistent with other causes of acute renal
failure. In patients who cannot collect a 24-hour specimen, typically small children, a uric acid creatinine ratio can be used to approximate 24-hour excretion. Pediatric Reference Ranges of Uric Acid/Creatinine (mg/mg)(2) Age (year) 5th Percentile 95th Percentile 0-0.5 >1.189 <2.378 0.5-1 >1.040 <2.229 1-2 >0.743 <2.080 2-3 >0.698 <1.932 3-5 >0.594 <1.635 5-7 >0.446 <1.189 7-10 >0.386 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594

Reference Values:
> or =18 years: <0.60 mg/mg creatinine.
Reference values have not been established for patients who are less than 18 years of age.

Clinical References:

Uroporphyrinogen Decarboxylase, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common porphyria resulting from a partial deficiency of hepatocyte or erythrocyte uroporphyrinogen decarboxylase (UROD; see The Heme Biosynthetic Pathway in Special Instructions). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in less than 5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests, with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma.

Useful For: Diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated, and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
> or =1.0 RU (normal)
0.80-0.99 RU (indeterminate)
<0.80 RU (indicative of PCT type II)
RU = Relative Units

Clinical References:
1. Tortorelli S, Kloke K, Raymond K: Chapter 15: Disorders of porphyrin

**Uroporphyrinogen Decarboxylase, Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Porphyrin cutanea tarda (PCT) is the most common porphyria resulting from a partial deficiency of hepatocyte or erythrocyte uroporphyrinogen decarboxylase (UROD; see The Heme Biosynthetic Pathway in Special Instructions). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in <5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests, with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma.

**Useful For:** Preferred test for the confirmation of a diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated, and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
- > or =1.0 RU (normal)
- 0.80-0.99 RU (indeterminate)
- <0.80 RU (indicative of PCT type II)
- RU = Relative Units

Uroporphyrinogen III Synthase (Co-Synthase), Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Congenital erythropoietic porphyria (CEP) is an extremely rare, autosomal recessive porphyria that typically presents in early infancy. Also known as Gunther disease, CEP results from a deficiency of uroporphyrinogen III (co-) synthase (UROIIIS). In most cases, the disorder is suggested during the first few days or weeks of life by pink, violet, or brown urinary staining of diapers. Clinical symptoms include hemolytic anemia, hepatosplenomegaly, skin photosensitivity, scarring and blistering, red or brown dental discoloration (erythrodontia), and hypertrichosis (excess body hair). Growth and cognitive developmental delays are commonly observed in individuals with CEP. A few cases of adult-onset CEP have been reported, typically associated with a myelodysplastic syndrome. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For: Diagnosis of congenital erythropoietic porphyria. This test is not useful for diagnosis of acute intermittent porphyria (AIP).

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
> or =75 Relative Units (normal)

See The Heme Biosynthetic Pathway in Special Instructions.


UroVysion for Detection of Bladder Cancer, Urine

Clinical Information: Cystoscopy and urine cytology have been the primary methods for detecting urothelial carcinoma (UC). Unfortunately urine cytology has relatively poor sensitivity for the detection of recurrent UC. This is problematic because patients who have undetected recurrent tumors may have tumor progression that places them at increased risk of developing metastatic UC. The UroVysion assay is a FISH assay for the detection of recurrent UC. The UroVysion probe set contains probes to the centromeres of chromosomes 3, 7, and 17, and a locus-specific probe to the 9p21 band (site of the P16 tumor suppressor gene). The UroVysion assay detects cells with chromosomal abnormalities that are consistent with a diagnosis of UC. Studies have shown that the assay has higher sensitivity than urine cytology but similar specificity for the detection of recurrent UC. The UroVysion assay also demonstrates higher specificity than the BTA-stat assay for recurrent UC.
Useful For: Monitoring for tumor recurrence in patients with a history of urothelial carcinoma involving the bladder or upper urinary tract Assessing patients with hematuria for urothelial carcinoma

Interpretation: Lower Tract Samples: Abnormal: any specimen satisfying 1 of the following criteria: -Four or more cells with gains of 2 or more chromosomes -Ten or more cells with a gain of a single chromosome or 10 or more cells with tetrasomic signal patterns (ie, 4 copies for each of the 4 probes) -Homozygous deletion of the 9p21 locus in 20% or more of the cells analyzed For cases that are abnormal, the percentage of abnormal cells and type of chromosomal abnormality (ie, polysomy, trisomy, tetrasomy, or homozygous 9p21 deletion) are indicated in the test report. Negative: -Fewer than 4 cells with gains of 2 or more chromosomes -Fewer than 10 cells with gain of a single chromosome or tetrasomy -Less than 20% of cells with homozygous 9p21 deletion Upper Tract Samples: Abnormal: any upper tract specimen satisfying 1 of the following criteria: -Four or more hypertetrasomy cells with at least 5 copies of 2 or more chromosomes -Ten or more cells with a gain of a single chromosome or 10% or more cells with tetrasomic or near-tetrasomic signal patterns (ie, 4 copies for each of the 4 probes) -Homozygous deletion of the 9p21 locus in 20% or more of the cells analyzed Negative: -Fewer than 4 cells with hypertetrasomy with at least 5 copies of 2 or more chromosomes -Fewer than 20% of cells with homozygous 9p21 deletion

Reference Values: An interpretive report will be provided.


USPF 58104

USP6 (17p13), Aneurysmal Bone Cyst and Nodular Fasciitis, FISH, Tissue

Clinical Information: Aneurysmal bone cyst (ABC) is a multicystic and expansile bone tumor of uncertain line of differentiation. USP6 rearrangements are detectable in approximately 70% of primary ABC and not in other conditions that may simulate ABC histologically, including giant cell tumor of bone, osteosarcoma, osteoblastoma, brown tumor, cherubism, and vascular neoplasms. Nodular fasciitis (NF) is a self-limited mesenchymal lesion of myofibroblastic differentiation. NFâs rapid growth, rich cellularity, and brisk mitotic activity may lead to a misdiagnosis of sarcoma. USP6 rearrangements are detectable in 90% of NF but not in other conditions that may simulate NF, including dermatofibroma, cellular fibrous histiocytoma, fibromatosis, and a large variety of sarcomas.

Useful For: Supporting the diagnosis of aneurysmal bone cyst or nodular fasciitis

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the USP6 FISH probe (positive result). A positive result is consistent with rearrangement of the USP6 gene locus on 17p13 and supports the diagnosis of aneurysmal bone cyst (ABC) or nodular fasciitis (NF). A negative result is consistent with no rearrangement of the USP6 gene locus on 17p13. However, this result does not exclude the diagnosis of ABC or NF. Rearrangement varies in individual tumors and among different cells in the same tumor.

Reference Values: An interpretive report will be provided.

Ustekinumab Quantitation with Antibodies, Serum

**Clinical Information:** Ustekinumab (UTK) is a fully human IgG1 kappa monoclonal antibody (1) that binds with high affinity to the p40 subunit of human interleukin (IL)12 and IL23 and has been approved for the treatment of patients with moderate to severe Crohn disease (CD), moderate to severe ulcerative colitis (UC), psoriatic arthritis, and plaque psoriasis. The drug prevents IL12 and IL23 bioactivity by binding and neutralizing the shared p40 subunit, preventing interaction with the cell surface receptor protein IL12Rbeta1. Through this mechanism of action, UTK effectively neutralizes IL12 and IL23, proteins that are thought to be associated with gastrointestinal inflammation in CD and UC. In the setting of the inflammatory bowel diseases (IBD), CD and UC, the treatment regimen is started with a single weight-based loading dose of the t-mab administered intravenously (IV), and a maintenance regimen with standard (non-weight based) subcutaneous administration of ustekinumab 8 weeks after induction dose, and every 8 weeks thereafter. There is very little data supporting proactive therapeutic drug monitoring for ustekinumab. The test is most useful in the evaluation of loss of response to therapy. A gradual decrease in efficacy over time following an initial response to biologics is common. In many cases, antibodies generated to the biologic are responsible for treatment failure, as they bind to the drug creating an immunocomplex and clearing the drug faster from circulation. For IBD, measurements in nonresponders are indicated at post-induction (week 8) and concentrations of ustekinumab associated with favorable outcomes are greater than 3.5 mcg/mL. In addition, for measurements during maintenance stages of therapy, ustekinumab concentrations > or =1 mcg/mL are associated with clinical response and clinical remission. At maintenance stages, ustekinumab concentrations > or =4.5 mcg/mL are associated with mucosal healing. In clinical trials, 6% to 12.4% of patients using ustekinumab for psoriasis or psoriatic arthritis developed antibodies-to-ustekinumab (ATU) over time. For IBD, between 2.9% and 4.6% of patients developed ATU when treated with ustekinumab for one year.(1) Therefore, it is important to monitor trough concentrations of serum UTK to correlate drug levels with loss of response to therapy. ATU may increase drug clearance in treated patients or neutralize the drug effect, thereby potentially contributing to the loss of response. ATU could also cause adverse events such as serum sickness and hypersensitivity reactions. Currently, ustekinumab quantitation is performed in conjunction with immunogenicity assessment for ATU.

**Useful For:** Evaluation of loss of response to therapy Quantification of ustekinumab in human serum Trough level quantitation for evaluation of patients treated with ustekinumab Detection of antibodies to ustekinumab in human serum

**Interpretation:** Antibodies to ustekinumab (ATU) absent ATU present Ustekinumab quantification <1.0 mcg/mL For nonresponders: Insufficient ustekinumab is present. In the absence of ATU, consider optimizing therapy by increasing the dose or shortening the administration intervals, or by adding an immunomodulator to the therapeutic regimen. For nonresponders: Insufficient ustekinumab is present. Antibodies-to-ustekinumab detected can contribute to faster clearance of ustekinumab and treatment failure. Clinical evaluation is recommended. Ustekinumab quantification > or =1.0 mcg/mL For nonresponders: If the sample was collected at trough ie, immediately before the next infusion, the results could suggest a mechanistic failure of ustekinumab. The provider may consider switching therapeutic regimen outside of the drug class. For nonresponders: If the sample was collected at trough ie, immediately before the next infusion, the results could suggest a mechanistic failure of ustekinumab. The provider may consider switching therapeutic regimen outside of the drug class.

**Reference Values:**

**USTEKINUMAB QN, S:** Limit of quantitation is 0.3 mcg/mL

In inflammatory bowel disease, at post-induction measurement (week 8), concentrations above 3.5 mcg/mL are associated with good outcomes

For maintenance stages:
Concentrations > or =1.0 mcg/mL are associated with clinical response and clinical remission
Concentrations > or =4.5 mcg/mL are associated with mucosal healing

USTEKINUMAB AB, S:
Limit of quantitation is 10 AU/mL
Absent: <10 AU/mL
Present: > or =10 AU/mL


Ustilago nuda, Mold Grain Rust, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Ustilago nuda, Mold Grain Rust, IgE Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Uveal Melanoma, Chromosome 3 Monosomy, FISH, Tissue**

**Clinical Information:** Uveal melanoma is the most common type of primary intraocular malignancy in adults, with an annual incidence of 6 per million. These melanomas arise within pigmented cells of the uveal tract of the eye, which consists of the choroid, ciliary body, and iris. Overall, mortality rates in patients with uveal melanoma are quite high (approximately 50%) and are due to metastatic disease. Identifying patients likely to develop metastasis is critical for establishing patient prognosis. Previous studies have demonstrated that monosomy 3 is highly correlated with the development of metastatic disease in patients with uveal melanoma.

**Useful For:** As an aid to prognosis in patients with uveal melanoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for chromosome 3 probe set. A positive result is consistent with monosomy 3 and a higher risk for metastatic disease in uveal melanoma patients. A negative result suggests that aneuploidy of chromosome 3 is not present.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FNSVG**

**Vaginitis (VG), NuSwab**

**Clinical Information:** This test is intended to be used as an aid to the diagnosis of bacterial vaginosis (BV) in women with a clinical presentation consistent with this disorder. The BV test utilizes semiquantitative PCR analysis of the three most predictive marker organisms (Atopobium vaginae, BVAB-2, and Megasphaera-1) to generate a total score that correlates directly with the presence or absence of BV. In this test system, samples with a score of 0 to 1 are considered negative for BV, samples with a score of 3 to 6 are positive for BV, and samples with a score of 2 are indeterminate for BV.

**Useful For:** Used to detect the presence of Candida albicans and Candida glabrata DNA in vaginal samples as an aid to the diagnosis of vulvovaginal candidiasis in symptomatic women. Also used in the diagnosis of Trichomonas vaginalis infections.

**Reference Values:**
Candida albicans, NAA: Negative
Candida glabrata, NAA: Negative
Trich vag by NAA: Negative

**VALPG**

**Valproic Acid, Free and Total, Serum**

**Clinical Information:** Valproic acid (valproate, Depakote, or Depakene) is an effective medication...
Valproic Acid, Free, Serum

**Clinical Information:** Valproate (valproate, Depakote, or Depakene) is an effective medication for absence seizures, generalized tonic-clonic seizures, and partial seizures, when administered alone or in conjunction with other antiepileptic agents. The valproic acid that circulates in blood is 85% to 90% protein-bound under normal circumstances. In uremia or during concomitant therapy with other drugs that are highly protein-bound (such as phenytoin), valproic acid is displaced from protein, resulting in a higher free fraction of the drug circulating in blood. Since neurologic activity and toxicity of valproic acid are directly related to the unbound fraction of drug, adjustment of dosage based on knowledge of the free valproic acid concentration may be useful in the following situations: concomitant use of highly protein-bound drugs (usually >80% bound), hypoalbuminemia, pregnancy, renal or hepatic failure, and in the elderly. In these situations, the total valproic acid concentration in the blood may underestimate the disproportionately higher free valproic acid fraction.

**Useful For:** Monitoring free valproic acid in therapy Assessing compliance Evaluating potential toxicity

**Reference Values:**

<table>
<thead>
<tr>
<th>VALPROIC ACID, TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic: 50 (trough)-125 (peak) mcg/mL</td>
</tr>
<tr>
<td>Critical value: &gt; or =151 mcg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VALPROIC ACID, FREE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic: 5-25 mcg/mL</td>
</tr>
<tr>
<td>Critical value: &gt;30 mcg/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**
Interpretation: The generally acceptable range for total valproic acid used as a reference to guide its therapy is 50 to 125 mcg/mL. The corresponding range of free valproic acid concentration for clinical reference is 5 to 25 mcg/mL. Low free valproic acid concentration relative to these ranges may suggest inadequate dosing, whereas, a high free valproic acid concentration may be associated with toxic effects. Because the concentration of valproic acid fluctuates considerably depending on the time from last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

Reference Values:
Therapeutic: 5-25 mcg/mL
Critical value: >30 mcg/mL


Valproic Acid, Total, Serum

Clinical Information: Valproic acid (valproate, Depakote, or Depakene) is used for treatment of simple and complex absence seizures and as combination therapy with other anticonvulsants for control of generalized seizures that include absence seizures. Valproic acid is initially dosed at 15 mg/kg/day, with dosage increases over time to a maximum of 60 mg/kg/day. The volume of distribution of valproic acid is 0.2 L/kg and its half-life is 10 to 14 hours in adults, and shorter in children. It is approximately 90% protein bound. Hepatic failure and a Reyes-like syndrome associated with administration of valproic acid at therapeutic levels have been reported. Careful monitoring of liver function during the first 6 months of therapy is required. Major side effects such as central nervous system depression, thrombocytopenia, and hepatic dysfunction are likely to be experienced if the peak level regularly is above 125 mcg/mL. Analysis of free valproic acid levels may be useful in delineating the cause of toxicity when the total concentration is not excessive. Valproic acid exhibits substantial effects on the pharmacology of phenytoin, whereas phenytoin exhibits only a limited effect on valproic acid. This is due to the relative abundance of the 2 drugs in the body. Valproic acid is present at a 2- to 3-fold mass excess and a 5- to 7-fold molar excess.

Useful For: Monitoring total valproic acid in therapy Assessing compliance Evaluating potential toxicity

Interpretation: Optimal response is usually observed when the trough level is above 50 mcg/mL. Peak levels should not exceed 125 mcg/mL.

Reference Values:
Therapeutic: 50 (trough)-125 (peak) mcg/mL
Critical value: > or =151 mcg/mL


Vancomycin, Peak, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and...
Vancomycin, Random, Serum

**Clinical Information:** Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta-lactam antibiotics. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients concomitantly medicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC determinations). These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

**Useful For:** Monitoring adequacy of drug concentration during vancomycin therapy whenever a specimen is submitted or collected without collection timing information

**Interpretation:** Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 and 20.0 mcg/mL, depending on the type of infection. Peak levels are not recommended for monitoring, except in select circumstances such as when performing pharmacokinetic analyses (eg, area under the curve: AUC determinations). Typical peak levels are between 20.0 and 45.0 mcg/mL. These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

**Reference Values:**
- Therapeutic: 20.0-45.0 mcg/mL

**Clinical References:**
**Vancomycin, Trough, Serum**

**Clinical Information:** Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta-lactam antibiotics. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high-risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

**Useful For:** Preferred test for monitoring vancomycin therapy Monitoring trough concentrations drawn at steady-state in selected patients receiving vancomycin therapy

**Interpretation:** Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 to 20.0 mcg/mL, depending on the type of infection. These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

**Reference Values:**
Therapeutic: 10.0-20.0 mcg/mL


**Vancomycin-Resistant Enterococcus, Molecular Detection, PCR, Varies**

**Clinical Information:** Vancomycin-resistant enterococci (VRE) are major nosocomial pathogens. Patients who are particularly vulnerable to fatal disease from VRE include those with hematologic malignancies and liver transplants. Nosocomial spread of VRE occurs as the result of fecal carriage. Risks for both colonization and infection include prolonged hospitalization, intensive care unit stay, transplantation, hematologic malignancies, and prolonged exposure to antibiotics. The Centers for Disease Control and Prevention provides recommendations to prevent the spread of VRE in institutional settings. These recommendations include isolation of patients experiencing active VRE infection, screening of patients by perianal swab or fecal testing to identify carriers of VRE, and subsequent isolation or cohorting of VRE carriers. Identification and isolation of VRE carriers has been shown to be
cost-effective. In Enterococcus faecalis or E faecium, vancomycin resistance is usually associated with the presence of vanA or vanB. The presence of these genes is detected by a molecular method in this assay.

**Useful For:** Identifying carriers of vancomycin-resistant enterococci

**Interpretation:** Positive test results indicate the presence of either vanA or vanB, which confer vancomycin resistance in Enterococcus faecalis and Enterococcus faecium (and occasionally other organisms). Patients with a positive test result should be placed in isolation or cohorted with other vancomycin-resistant enterococci (VRE) carriers according to the institution’s infection control practices. A negative result indicates the absence of detectable vanA or vanB DNA, but does not rule-out carrier status and may occur due to inhibition of polymerase chain reaction (PCR), sequence variability underlying primers or probes, or the presence of VRE DNA in quantities less than the limit of detection of the assay. In the rare event that PCR testing appears to be negative but there is evidence of PCR inhibition, the result will read "PCR inhibition present." In such cases, a new specimen should be submitted for repeat testing.

**Reference Values:**
Not applicable

**Clinical References:**

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**FVANG**

**Vanilla IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**VANIL**

**Vanilla, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing the diagnosis of an allergy to vanilla Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**Vanillylmandelic Acid and Homovanillic Acid, Random, Urine**

**Clinical Information:** Elevated values of homovanillic acid (HVA), vanillylmandelic acid (VMA), and other catecholamine metabolites (eg, dopamine) may be suggestive of the presence of a catecholamine-secreting tumor (eg, neuroblastoma, pheochromocytoma, or other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism: monamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** First preferred test for screening for catecholamine-secreting tumors in a random urine specimen when requesting both homovanillic acid and vanillylmandelic acid Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

**Interpretation:** Homovanillic acid (HVA) and vanillylmandelic acid (VMA) concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA and VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

**Reference Values:**

<table>
<thead>
<tr>
<th>VANILLYLMANDELIC ACID</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year: &lt;25.0 mg/g creatinine</td>
</tr>
</tbody>
</table>
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years: <7.0 mg/g creatinine

**HOMOVANILIC ACID**
<1 year: <35.0 mg/g creatinine
1 year: <30.0 mg/g creatinine
2-4 years: <25.0 mg/g creatinine
5-9 years: <15.0 mg/g creatinine
10-14 years: <9.0 mg/g creatinine
> or =15 years: <8.0 mg/g creatinine

**Clinical References:**

Vanillylmandelic Acid, 24 Hour, Urine

**Clinical Information:** Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid: HVA and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of 1 of the above-mentioned tumors.

**Useful For:** Screening children for catecholamine-secreting tumors with a 24-hour urine collection when requesting testing for only vanillylmandelic acid Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

**Interpretation:** Vanillylmandelic acid and/or homovanillic acid concentrations are elevated in most patients (more than 90%) with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated values are suggestive of a pheochromocytoma, but they are not diagnostic.

**Reference Values:**
<1 year: <25.0 mg/g creatinine
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years (adults): <8.0 mg/24 hours

**Clinical References:**
**VMAR**

**Vanillylmandelic Acid, Random, Urine**

**Clinical Information:** Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid: HVA and dopamine) are typically elevated in patients with catecholamine-secreting tumors (e.g., neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of one of the above-mentioned tumors.

**Useful For:** Screening children for catecholamine-secreting tumors with a random urine collection when requesting vanillylmandelic acid only Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

**Interpretation:** Vanillylmandelic acid (VMA) and/or homovanillic acid concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

**Reference Values:**
- <1 year: <25.0 mg/g creatinine
- 1 year: <22.5 mg/g creatinine
- 2-4 years: <16.0 mg/g creatinine
- 5-9 years: <12.0 mg/g creatinine
- 10-14 years: <8.0 mg/g creatinine
- > or =15 years (adults): <7.0 mg/g creatinine

**Clinical References:**

**VZV**

**Varicella Zoster Virus (VZV) Immunostain, Technical Component Only**

**Clinical Information:** Varicella zoster virus (VZV) is a member of the herpes virus family and is the etiological agent for varicella (chicken pox) and herpes zoster (shingles). The immunostain for VZV uses a cocktail of antibodies that recognizes several glycoproteins, the nucleocapsid protein, and the immediate early protein of the virus.

**Useful For:** Aids in the identification of varicella zoster virus infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full
diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Varicella-Zoster Antibody, IgG, Serum

Clinical Information: Varicella-zoster virus (VZV), a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and herpes zoster (shingles). Chickenpox is a highly contagious, though typically benign disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure.(1) Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity.(2) Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement.(2,3) Serologic screening for IgG-class antibodies to VZV aids in identifying nonimmune individuals.

Useful For: Determination of immune status of individuals to the varicella-zoster virus (VZV)

Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

Interpretation: Positive: Antibody index (AI) value of 1.1 or higher: The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies indicates prior exposure to the varicella-zoster virus (VZV) through infection or immunization. Individuals testing positive are considered immune to varicella-zoster. Equivocal: AI 0.9-1.0 Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI of 0.8 or lower The absence of detectable IgG-class antibodies suggests no prior exposure to the VZV or the lack of a specific immune response to immunization.

Reference Values:
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

Varicella-Zoster Antibody, IgM and IgG, Serum

Clinical Information: Varicella-zoster virus (VZV), a herpesvirus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious, though typically benign disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. (1) Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. (2) Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. (2,3) Serologic screening for IgG-class antibodies to VZV will aid in identifying nonimmune individuals. The presence of IgM-class antibodies to VZV is suggestive of acute or recent infection however results should be correlated with clinical presentation.

Useful For: Laboratory diagnosis of acute and recent infection with varicella-zoster virus (VZV)
Determination of immune status of individuals to the VZV Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

Interpretation: A positive IgG result coupled with a positive IgM result suggests recent infection with varicella-zoster virus (VZV). This result should not be used alone to diagnose VZV infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with VZV. These individuals are considered to have protective immunity to re-infection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to VZV and nonimmunity. However, a negative result does not rule-out VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infections should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

Reference Values:

IgM
Negative
Reference values apply to all ages.

IgG
Vaccinated: positive (> or =1.1 AI)
Unvaccinated: negative (< or =0.8 AI)
Reference values apply to all ages.

(rash-associated) diseases, chickenpox and herpes zoster (shingles). Chickenpox is a highly contagious disease usually contracted during childhood and is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure.(1). Although primary infection results in immunity to subsequent exposure to chickenpox, the virus remains latent in the body, localized to the dorsal root or cranial nerve ganglia. Reactivation of latent infection manifests as herpes zoster. On reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash usually limited to a single dermatome. Reactivation occurs in older adults and in patients with impaired cellular immunity.(2) Several populations are at risk of suffering unusually severe reactions to VZV infections. The infection in pregnant women may spread through the placenta to the fetus causing congenital disease in the infant. Immunocompromised patients in hospitals may contract severe nosocomial infections from others who have active VZV infections are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement.(2,3). Therefore, serologic screening of direct health care providers (physicians, allied health care personnel) and individuals in high-risk groups is necessary to avoid uncontrolled spread of infection. While the clinical presentation of VZV infection is generally characteristic, serologic evaluation of patients with atypical and systemic infections is often required. For example, it is extremely important to serologically evaluate patients for the early detection of VZV infections in hospital settings. Nosocomial spread of VZV infection can be life-threatening to immunocompromised patients susceptible to infection.

**Useful For:** Diagnosing acute-phase infection with varicella-zoster virus

**Interpretation:** A positive IgM result indicates a recent infection with varicella-zoster virus (VZV). A negative result does not rule out the diagnosis of VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infection should be followed by testing a new specimen in 2 to 3 weeks.

**Reference Values:**
- Negative
- Reference values apply to all ages.

**Clinical References:**

**FVZGC 58045**

**Varicella-Zoster Virus Antibody, IgG, CSF**

**Interpretation:** The detection of antibodies to varicella-zoster in CSF may indicate central nervous system infection. However, consideration must be given to possible contamination by blood or transfer of serum antibodies across the blood-brain barrier.

**Reference Values:**
- 134.9 IV or less: Negative - No significant level of IgG antibody to varicella-zoster virus detected.
- 135.0 - 164.9 IV: Equivocal - Repeat testing in 10 - 14 days may be helpful.
- 165.0 IV or greater: Positive - IgG antibody to varicella-zoster virus detected, which may indicate a current or past varicella-zoster infection.

**LVZV 81241**

**Varicella-Zoster Virus, Molecular Detection, PCR, Varies**

**Clinical Information:** Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before 10 years of age. After primary infection with VZV, the virus persists in latent form and may emerge clinically (usually in adults 50 years of age and older) to cause a unilateral...
vesicular eruption, generally in a dermatomal distribution (shingles).

**Useful For:** Rapid (qualitative) detection of varicella-zoster virus DNA in clinical specimens for laboratory diagnosis of disease due to this virus

**Interpretation:** Detection of varicella-zoster virus (VZV) DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler PCR assay does not yield positive results with other herpesvirus gene targets (herpes simplex virus, cytomegalovirus, Epstein-Barr virus).

**Reference Values:**

- Negative

**Clinical References:**

**VEGF**

**Vascular Endothelial Growth Factor, Plasma**

**Clinical Information:** Vascular endothelial growth factor (VEGF) is a critical modulator of angiogenesis (the growth of new blood vessels). (1) In mammals, there are 5 members of the VEGF family, with VEGF-A being the most well-studied. VEGF-A promotes angiogenesis by inducing migration of endothelial cells, promoting mitosis of endothelial cells, and upregulating matrix metalloproteinase activity. (2) VEGF-A is regulated by hypoxia, with increased expression when cells detect an environment low in oxygen. Physiologically, VEGF induces new blood vessel formation during embryonic development, after tissue injury, and in response to blocked vessels. VEGF also regulates pathological vessel formation, such as in tumor growth and metastases. Angiogenesis during tumor development is complex, although it is clear that VEGF plays a key role. VEGF also regulates angiogenesis in other disease states including rheumatoid arthritis (RA), osteoarthritis, diabetes, and age-related macular degeneration. (3) In addition, circulating concentrations of VEGF are elevated in patients with polynuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, a monoclonal plasma cell disorder. (4) Although the pathologic role of VEGF in POEMS is unclear, it is a useful diagnostic marker for assessing response to therapy.

**Reference Values:**

- < or = 96.2 pg/mL

**Clinical References:**

**VIP**

**Vasoactive Intestinal Polypeptide, Plasma**

Current as of June 14, 2021 12:13 pm CDT
**Clinical Information:** Vasoactive intestinal polypeptide (VIP) was originally isolated from porcine small intestine and was recognized by its potent vasodilator activity. This brain/gut hormone has widespread distribution and is present in neuronal cell bodies localized in the central nervous system, digestive, respiratory, and urogenital tracts, and exocrine, thyroid, and adrenal glands. VIP has a wide scope of biological actions. The main effects of VIP include relaxation of smooth muscle (bronchial and vascular dilatation), stimulation of gastrointestinal water and electrolyte secretion, and release of pancreatic hormones. VIP-producing tumors (VIPomas) are rare; most (90%) are located in the pancreas. Watery diarrhea, hypokalemia, and achlorhydria are key symptoms.

**Useful For:** Detection of vasoactive intestinal polypeptide producing tumors in patients with chronic diarrheal diseases

**Interpretation:** Values above 75 pg/mL may indicate the presence of an enteropancreatic tumor causing hypersecretion of vasoactive intestinal polypeptide (VIP). Values above 200 pg/mL are strongly suggestive of VIP-producing tumors (VIPoma). VIPoma is unlikely with a 24-hour stool volume below 700 mL.

**Reference Values:**

<75 pg/mL

**Clinical References:**

**Vasoactive Intestine Polypeptide (VIP), Technical Component Only**

**Clinical Information:** Excessive vasoactive intestine polypeptide (VIP) production by islet cell tumors has been associated with Verner-Morrison syndrome, also known as pancreatic cholera, in which patients have massive, watery diarrhea. A subset of normal cells in the pancreatic islets express VIP (<1%). Peripheral nerves and ganglion cells also serve as a positive internal control.

**Useful For:** Aiding in the identification of islet cell tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**VDRL Titer, Spinal Fluid**

**Clinical Information:** VDRL is a nontreponemal serologic test for syphilis that uses a cardiolipin-cholesterol-lecithin antigen to detect reaginic antibodies. The presence of neurosyphilis in untreated patients can be detected by the presence of pleocytosis, elevated protein, and a positive VDRL.

**Useful For:** Aiding in the diagnosis of neurosyphilis

**Interpretation:** A positive VDRL on spinal fluid is highly specific for neurosyphilis.

**Reference Values:**
Only orderable as a reflex. For more information see VDSF / VDRL, Spinal Fluid.

Negative
Reference values apply to all ages.

**Clinical References:**

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**VDRL, Spinal Fluid**

**Clinical Information:** VDRL is a nontreponemal serologic test for syphilis that uses a cardiolipin-cholesterol-lecithin antigen to detect reaginic antibodies. The VDRL test performed on cerebrospinal fluid (CSF) can be used to diagnose neurosyphilis in patients with a prior history of syphilis infection. The presence of neurosyphilis in untreated patients can be detected by the presence of pleocytosis, elevated protein, and a positive VDRL.

**Useful For:** Aiding in the diagnosis of neurosyphilis

**Interpretation:** A positive VDRL result on spinal fluid is highly specific for neurosyphilis. A single negative VDRL result should not be used to exclude neurosyphilis and repeat testing on a new specimen may be necessary. Positive results will be titered.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

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**Vedolizumab Quantitation with Antibodies, Serum**

**Clinical Information:** Vedolizumab (Entyvio) is a humanized monoclonal antibody directed against integrin alpha-4 beta-7. Blocking the alpha-4 beta-7 integrin results in a gut-selective anti-inflammatory response. The drug is FDA-approved for the treatment of adult patients with moderately to severely active ulcerative colitis or Crohn disease. Although optimal therapeutic concentrations of vedolizumab are not well known, Mayo Clinic Gastroenterologists are working to correlate drug concentrations with patient outcomes. Vedolizumab testing will assess the patients loss of response to therapy, similar to therapy received using tumor necrosis factor (TNF) inhibitors, such as infliximab and adalimumab. Some patients on vedolizumab may develop antibodies to vedolizumab (ATV) over time. In clinical trials, approximately 4% of patients treated with vedolizumab were positive for ATV at any time and 1% or less were persistently positive. Therefore, simultaneous testing for measurement of ATV is recommended. ATV uses a bridging immunoassay on an electrochemiluminescence (Mesoscale Discovery) platform.
Useful For: Assessing the unexpected loss of response to therapy with vedolizumab over time An aid to achieving desired serum levels of vedolizumab

Interpretation: Data in the literature with association of vedolizumab trough levels and improved outcomes is still scarce. The limit of quantitation of the test is 2.0 mcg/mL. In a retrospective Mayo Clinic study conducted from 2016-2017 with 171 patients (62% Crohn disease, 31% ulcerative colitis, and 7% indeterminate colitis), the median vedolizumab trough concentration was 15.3 mcg/mL. Minimum trough (immediately before next infusion) therapeutic concentrations of vedolizumab are expected to be above 15 mcg/mL.

Reference Values:
VEDOLIZUMAB QUANTITATION:
Vedolizumab lower limit of quantitation=2.0 mcg/mL

VEDOLIZUMAB ANTIBODIES:
Antibodies to vedolizumab: <9.8 ng/mL


VEDOLIZUMAB QUANTITATION with Reflex to Antibodies, Serum

Clinical Information: Vedolizumab (Entyvio) is a humanized monoclonal antibody directed against integrin alpha-4 beta-7. Blocking the alpha-4 beta-7 integrin results in a gut-selective anti-inflammatory response. The drug is FDA-approved for the treatment of adult patients with moderately to severely active ulcerative colitis or Crohn disease. Although optimal therapeutic concentrations of vedolizumab are not well known, Mayo Clinic Gastroenterologists are working to correlate drug concentrations with patient outcomes. Vedolizumab testing will assess the patients loss of response to therapy, similar to therapy received using tumor necrosis factor (TNF) inhibitors, such as infliximab and adalimumab. Some patients on vedolizumab may develop antibodies to vedolizumab (ATV) over time. In clinical trials, approximately 4% of patients treated with vedolizumab were positive for ATV at any time and 1% or less were persistently positive. Therefore, simultaneous testing for measurement of ATV is recommended. ATV uses a bridging immunoassay on an electrochemiluminescence (Mesoscale Discovery) platform.

Useful For: Assessing the response to therapy with vedolizumab An aid to achieving desired trough serum levels of vedolizumab Monitoring patient compliance

Interpretation: Data in the literature with association of vedolizumab trough levels and improved outcomes is still scarce. The limit of quantitation of the test is 2.0 mcg/mL. In a retrospective Mayo Clinic study conducted from 2016-2017 with 171 patients (62% Crohn disease, 31% ulcerative colitis, and 7% indeterminate colitis), the median vedolizumab trough concentration was 15.3 mcg/mL. Minimum trough (immediately before next infusion) therapeutic concentrations of vedolizumab are expected to be above 15 mcg/mL.
**Reference Values:**

**VEDOLIZUMAB QUANTITATION:**
Vedolizumab lower limit of quantitation: 2.0 mcg/mL

**VEDOLIZUMAB ANTIBODIES:**
Antibodies to vedolizumab: <9.8 ng/mL

**Clinical References:**

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**Velvet Leaf, IgE, Serum**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:**
Establishing a diagnosis of an allergy to velvet leaf Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:**
Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

**FVENE**  
Venison IgE  
Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 Positive 4 17.50 - 49.99 Strong Positive 5 50.00 - 99.99 Very Strong Positive 6 >99.99 Very Strong Positive  
Reference Values: 
<0.35 kU/L

**VENLA**  
Venlafaxine, Serum  
Clinical Information: Venlafaxine is a serotonin and norepinephrine reuptake inhibitor approved for treatment of major depression, anxiety and panic disorders, and social phobias. It is also used for bipolar disorder, bulimia, post-traumatic stress, obsessive behavior, and attention-deficit disorder. Venlafaxine is converted by cytochrome P450 (CYP) 2D6 to the active metabolite, O-desmethylvenlafaxine. The therapeutic range for venlafaxine includes measurement if O-desmethylvenlafaxine; optimal response is seen when combined concentrations of parent and metabolite are between 195 and 400 ng/mL. Venlafaxine is significantly affected by reduced hepatic function but only slightly by reduced renal function. Average elimination half-lives are 5 hours for venlafaxine and 10 hours for O-desmethylvenlafaxine, which are much shorter than many other antidepressants. For this reason, extended release formulations are available. Time to peak serum concentration is 2 hours for the regular product and 8 hours for the extended release product. Common toxicities are mild, including drowsiness, dizziness, nausea, and headache.  
Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity Evaluating patient compliance  
Interpretation: Most individuals display optimal response to venlafaxine when combined serum levels of venlafaxine and O-desmethylvenlafaxine are between 195 and 400 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels greater than 800 ng/mL. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).  
Reference Values: 
Venlafaxine + O-desmethylvenlafaxine: 195-400 ng/mL  

**FBMBL**  
Venom Bumble Bee (Bombus terrestrus) IgE  
Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

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**FHOBG 57714**

**Venom Honey Bee IgG**

**Reference Values:**
>3.5 mcg/mL

Venom IgG Reference Values: 1.0 Åæ, 3.5 mcg/mL Low venom IgG indicating a significant reaction risk. 3.5 Åæ, 6.0 mcg/mL Moderate level of venom IgG that may be associated from serious sting reactions (J.Clin.Immun.6:172, 1983) > 6.0 mcg/mL Elevated venom IgG usually associated with protection from serious sting reactions (J.Clin.Immun.6:172, 1983) The interpretative guidelines have been adapted from Golden et al (JACI 1992; 90:386-393). The test method used is the Phadia ImmunoCAP IgG assay which has been recalibrated to correlate with the venom IgG assay referenced above.

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**FWFHG 57799**

**Venom W-F Hornet IgG**

**Reference Values:**
>3.5 mcg/mL

Venom IgG Reference Values: 1.0 Åæ, 3.5 mcg/mL Low venom IgG indicating a significant reaction risk. 3.5 Åæ, 6.0 mcg/mL Moderate level of venom IgG that may be associated from serious sting reactions (J.Clin.Immun.6:172, 1983) > 6.0 mcg/mL Elevated venom IgG usually associated with protection from serious sting reactions (J.Clin.Immun.6:172, 1983) The interpretative guidelines have been adapted from Golden et al (JACI 1992; 90:386-393). The test method used is the Phadia ImmunoCAP IgG assay which has been recalibrated to correlate with the venom IgG assay referenced above.

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**VLCZ 35571**

**Very Long Chain Acyl-CoA Dehydrogenase Deficiency, Full Gene Analysis, Varies**

**Clinical Information:** Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is an autosomal recessive disorder of mitochondrial fatty acid beta-oxidation. Mitochondrial beta-oxidation plays a major role in energy production and VLCAD catalyzes the first step in the breakdown of fatty acids that are 14 to 20 carbons long. VLCAD deficiency has a reported incidence of approximately 1 in 30,000 births and has a variable age of onset that is generally classified into 3 categories. Individuals with the early-onset type present with cardiomyopathy, hypotonia, and hepatomegaly in the first months of life; sudden death is also frequent. Individuals with the early-childhood onset type typically present with hypoketotic hypoglycemia and hepatomegaly without cardiomyopathy. Individuals with the late-onset type of VLCAD deficiency generally present after childhood with intermittent rhabdomyolysis and muscle dysfunction that often manifests as muscle cramps and exercise intolerance. Review of clinical features and biochemical analysis via plasma acylcarnitines, plasma fatty acid profile, urine organic acids, and fibroblast fatty acid oxidation probe studies are recommended as laboratory evaluations for VLCAD deficiency. Plasma and urine biochemical testing are not reliable for identifying all individuals with VLCAD deficiency or confirming carrier status, as biochemical findings may normalize during periods of good metabolic control. It is uncertain whether skin fibroblast analysis can identify carriers of VLCAD deficiency. The diagnosis is confirmed by molecular testing. Mutations in the ACADVL gene are responsible for VLCAD deficiency. Most mutations are family specific with the exception of the V283A
mutation (also reported in the literature as V243A). This mutation is estimated to account for 20% of pathogenic alleles in patients identified by newborn screening. When this test is ordered, results of biochemical assays should be included with the specimen as they are necessary for accurate interpretation of the VLCAD sequence analysis.

**Useful For:** Confirmation of a diagnosis of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency Carrier screening in cases where there is a family history of VLCAD deficiency, but an affected individual is not available for testing or disease-causing mutations have not been identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**VHL Gene, Erythrocytosis, Mutation Analysis, Varies**

**Clinical Information:** Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera, or secondary, in response to increased serum erythropoietin levels). Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and paraganglioma formation. It is caused by mutations in several genes, including VHL, and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and VHL can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL typically have normal p50 results. The true prevalence of hereditary erythrocytosis causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate-mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of
HIF proline residues. Mutations resulting in altered VHL proteins can lead to familial erythrocytosis, type 2 (ECYT2; OMIM 263400). ECYT2 is a clinically heterogeneous disorder characterized by congenital erythrocytosis with or without high serum EPO levels, venous and arterial thrombosis, and pulmonary hypertension that can manifest as early as infancy but more typically into adulthood. An increased risk for tumors associated with von Hippel-Lindau syndrome, which is also caused by mutations in the VHL gene, has not been observed.

Useful For: Diagnosis of suspected JAK2-negative VHL-related erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

An interpretive report will be provided.

remaining intact copy of VHL is somatically inactivated in target tissues (2-hit model). Sporadic cRCC, unrelated to VHL disease, also shows somatic deletions, sequence variants, or aberrant methylation in 80% to 100% of cases. Retinal angioma, CHB, and SHB cause morbidity and some mortality through pressure on adjacent structures and through retinal or subarachnoid hemorrhages. VHL-related cRCC and PC follow a similar clinical course as their sporadic counterparts, with substantial morbidity and mortality. Early detection of VHL-related tumors can reduce these adverse outcomes, and surveillance of affected individuals is, therefore, widely advocated. Genetic testing is the most accurate way to identify presymptomatic individuals, who can then be entered into a surveillance program. Research has suggested that certain combinations of VHL tumors cluster in VHL families, and this may be driven by the type of VHL gene variant present in the family. This observation has led to a phenotype-based classification of VHL syndrome. However, it should be noted that these patterns are not clear cut, and should not necessarily be used for diagnostic or therapeutic purposes. VHL Type 1: Retinal angioma, central nervous system (CNS) hemangioblastoma, renal cell carcinoma, pancreatic cysts, and neuroendocrine tumors. Low risk for pheochromocytoma. Associated with pathogenic truncating or missense variants that are predicted to grossly disrupt the folding of VHL protein. VHL Type 2: Pheochromocytoma, retinal angiomas, and CNS hemangioblastoma. High risk for pheochromocytoma. Associated with pathogenic missense variants. VHL Type 2 is further subdivided: -Type 2A: Pheochromocytoma, retinal angiomas, and CNS hemangioblastomas; low risk for renal cell carcinoma -Type 2B: Pheochromocytoma, retinal angiomas, CNS hemangioblastomas, pancreatic cysts, and neuroendocrine tumor; high risk for renal cell carcinoma -Type 2C: Risk for pheochromocytoma only Additionally, pathogenic sequence variants distinct from those associated with VHL syndrome can cause hereditary erythrocytosis or polycythemia. Cases of VHL disease and erythrocytosis are largely mutually exclusive, and patients who present with erythrocytosis do not typically develop the neoplasms discussed above, although they are sometimes associated with varicose veins and vertebral hemangiomas. Erythrocytosis due to VHL is caused by germline homozygous or compound heterozygous pathogenic sequence variants, and is inherited in an autosomal recessive manner. These patients usually have a markedly high erythropoietin level in the presence of an elevated hematocrit. Erythrocytosis due to a germline homozygous missense variant at nucleotide c.598C->T, p.R200W in the VHL gene has been found endemically in the Chuvash region of Russia, leading individuals with this variant to be labeled as having Chuvash polycythemia (CP), although further studies have determined that this variant can be found in other ethnic groups as well. These patients are at an increased risk to develop cerebrovascular and embolic complications. Heterozygous carriers are typically unaffected.

Useful For: Diagnosis of suspected von Hippel-Lindau (VHL) disease Diagnosis of suspected VHL-related hereditary erythrocytosis

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.


Vibrio Culture, Feces

**Clinical Information:** Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals), and infection with or exposure to one of these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician determine the appropriate testing to be performed. Vibrio cholerae, the causative agent of endemic, epidemic, and pandemic cholera, results in large volumes of rice-water stools due to the production of an enterotoxin. Severe dehydration is of concern in patients without access to adequate medical care. In the United States, Vibrio parahaemolyticus is the most common cause of Vibrio disease. V parahaemolyticus is associated with the consumption of raw shellfish or fish and results in gastroenteritis with nausea, vomiting, abdominal cramps, low-grade fever, and chills. Usually rehydration is the only treatment required, although in some cases, antimicrobial therapy is needed.

**Useful For:** Determining whether Vibrio species may be the cause of diarrhea. This test is generally not useful for patients that have been hospitalized for more than 3 days because the yield from these patients' specimens is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

**Interpretation:** The growth of Vibrio species identifies a potential cause of diarrhea.

**Reference Values:**
No growth of pathogen


Vigabatrin (Sabril)

**Reference Values:**

Units: ug/mL

Therapeutic and toxic ranges have not been established.

Expected serum vigabatrin concentrations in patients receiving recommended daily dosages: 20 &lt;ư&lt; 160 ug/mL

Vimentin Immunostain, Technical Component Only

**Clinical Information:** Vimentin is an intermediate filament protein (57 kD) present in cells of mesenchymal origin. A number of tumors coexpress vimentin and cytokeratin (eg, thyroid carcinomas, pleomorphic adenomas of the salivary glands, and some renal carcinomas). Coexpression of desmin and vimentin has also been reported in a number of soft tissue tumors (eg, rhabdomyosarcomas, leiomyosarcomas and alveolar soft tissue sarcomas).

**Useful For:** Identification of cells of mesenchymal origin in normal and neoplastic tissues
**Interpretation:** This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


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**VIRNR**

**87266**

**Viral Culture, Non-Respiratory, Varies**

**Clinical Information:** Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus (CMV), enteroviruses, herpes simplex virus (HSV), and varicella-zoster virus (VZV). Many viral infections (eg, HSV, CMV, VZV) can now be treated with antiviral drugs. Early laboratory diagnosis by isolation is very helpful in the medical management of these patients. Viruses that are detected in cell culture include: adenovirus, CMV, enterovirus, HSV, and VZV. Viruses that are not detected in cell culture include: Epstein-Barr virus, rubella virus (must order serology), West Nile virus, human papillomavirus, Norwalk virus or norovirus.

**Useful For:** Diagnosing viral infections in nonrespiratory specimens This test is not useful for viruses that cannot be detected in cell culture including: Epstein-Barr virus, rubella virus (order serology), West Nile virus, human papillomavirus, Norwalk virus or norovirus.

**Interpretation:** A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of this finding. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by this culture test include Epstein-Barr virus, rubella virus, papilloma, and Norwalk virus), and nonviable organisms submitted. For patients with diarrhea, see Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for other diagnostic tests that may be useful.

**Reference Values:**
Negative
If positive, virus is identified.


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**SVIR**

**45472**

**Viral Smear, Shell Vial (Bill Only)**

**Reference Values:**

**Current as of June 14, 2021 12:13 pm CDT**
800-533-1710 or 507-266-5700 or mayocliniclabs.com
This test is for billing purposes only.
This is not an orderable test.

**VISCS**

**8168**

**Viscosity, Serum**

**Clinical Information:** Viscosity is the property of fluids to resist flow. Hyperviscosity may be manifested by nasal bleeding, blurred vision, headaches, dizziness, nystagmus, deafness, diplopia, ataxia, paresthesias, or congestive heart failure. Funduscopic examination reveals dilation of retinal veins and flame shaped retinal hemorrhages. The most common cause of serum hyperviscosity is the presence of large concentrations of IgM monoclonal proteins, and Waldenstrom's macroglobulinemia accounts for 80% to 90% of hyperviscosity cases. Hyperviscosity syndrome can also occur in multiple myeloma patients. Because the ability of a monoclonal protein to cause hyperviscosity is affected by its concentration, molecular weight, and aggregation, sera with concentrations of monoclonal IgM greater than 4 g/dL, IgA greater than 5 g/dL, or IgG greater than 6 g/dL should be tested for hyperviscosity. Serum viscosity and electrophoresis are recommended before and after plasmapheresis in order to correlate viscosity and M-spike with patient symptoms. This correlation may be useful for anticipating the need for repeat plasmapheresis.

**Useful For:** Detection of increased viscosity Monitoring patients with hyperviscosity syndrome

**Interpretation:** Although viscosities greater than 1.5 centipoises (cP) are abnormal, hyperviscosity is rarely present unless the viscosity is greater than 3 cP.

**Reference Values:**
> or =16 years: < or =1.5 centipoises
Reference values have not been established for patients that are <16 years of age.


**VITAE**

**605267**

**Vitamin A and Vitamin E, Serum**

**Clinical Information:** Vitamin A: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene ingested and absorbed by the intestine (carotene is converted to vitamin A by intestine absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia), which can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, with an increased incidence of death related to infectious diseases. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day, and in children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcaemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension and bone demineralization may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg. Vitamin E (alpha-tocopherol): Vitamin E contributes to the normal maintenance of biomembranes, the vascular and nervous systems, and provides antioxidant protection for vitamin A. The level of vitamin E in the plasma or serum after a 12- to 14-hour fast reflects the individual's reserve status. The current understanding of the specific actions of vitamin E is very
incomplete. The tocopherols (vitamin E and related fat-soluble compounds) function as antioxidants and free-radical scavengers, protecting the integrity of unsaturated lipids in the biomembranes of all cells and preserving retinol from oxidative destruction. Vitamin E is known to promote the formation of prostacyclin in endothelial cells and to inhibit the formation of thromboxanes in thrombocytes, thereby minimizing the aggregation of thrombocytes at the surface of the endothelium. Those influences on thrombocyte aggregation may be of significance in relation to risks for coronary atherosclerosis and thrombosis. Deficiency of vitamin E in children leads to reversible motor and sensory neuropathies; this problem also has been suspected in adults. Premature infants who require an oxygen-enriched atmosphere are at increased risk for bronchopulmonary dysplasia and retrolental fibroplasia. Supplementation with vitamin E has been shown to lessen the severity of, and may even prevent, those problems. In addition, low blood levels of vitamin E may be associated with abetalipoproteinemia, presumably as a result of a lack of the ability to form very low-density lipoproteins and chylomicrons in the intestinal absorptive cells of affected persons. Vitamin E toxicity has not been established clearly. Chronically excessive ingestion has been suspected as a cause of thrombophlebitis, although this has not been definitively verified. Deficiencies of vitamins A and E may arise from poor nutrition or from intestinal malabsorption. Persons at risk, especially children, include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia. Infantile cholangiopathies that may lead to malabsorption of vitamins A and E include intrahepatic dysplasia and rubella-related embryopathy.

**Useful For:**
- Diagnosing vitamin A deficiency and toxicity
- Evaluating persons with intestinal malabsorption of lipids
- Evaluating individuals with motor and sensory neuropathies for vitamin E deficiency
- Monitoring vitamin E status of premature infants requiring oxygenation

**Interpretation:**
- Vitamin A: The World Health Organization recommends supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity. Vitamin E (alpha-tocopherol): Therapeutic Ranges: 0-17 years: 3.8 - 18.4 mg/L > or =18 years: 5.5 - 17.0 mg/L
- Significant deficiency: <3.0 mg/L

**Reference Values:**

**VITAMIN A (RETINOL)**
- 0-6 years: 11.3-64.7 mcg/dL
- 7-12 years: 12.8-81.2 mcg/dL
- 13-17 years: 14.4-97.7 mcg/dL
- > or =18 years: 32.5-78.0 mcg/dL

**VITAMIN E (ALPHA-TOCOPHEROL)**
- 0-17 years: 3.8-18.4 mg/L
- > or =18 years: 5.5-17.0 mg/L

**Clinical References:**

**Vitamin A, Serum**

**Clinical Information:**
The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene (provitamin A) ingested and absorbed by the intestine (carotene is converted to vitamin A by intestinal absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be
followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, where an increased incidence of death is associated with deficient vitamin A levels. Increased susceptibility is associated with vitamin A deficiency. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day and children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg.

**Useful For:** Diagnosing vitamin A deficiency and toxicity Monitoring vitamin A therapy

**Interpretation:** The World Health Organization recommendations supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity.

**Reference Values:**
- 0-6 years: 11.3-64.7 mcg/dL
- 7-12 years: 12.8-81.2 mcg/dL
- 13-17 years: 14.4-97.7 mcg/dL
- > or =18 years: 32.5-78.0 mcg/dL


**Vitamin A, Serum**

**Clinical Information:** The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene (provitamin A) ingested and absorbed by the intestine (carotene is converted to vitamin A by intestinal absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, where an increased incidence of death is associated with deficient vitamin A levels. Increased susceptibility is associated with vitamin A deficiency. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day and children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess.
excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg.

**Useful For:** Diagnosing vitamin A deficiency and toxicity Monitoring vitamin A therapy

**Interpretation:** The World Health Organization recommends supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity.

**Reference Values:**
Only orderable as part of a profile. For more information see VITAE / Vitamin A and Vitamin E, Serum.

- 0-6 years: 11.3-64.7 mcg/dL
- 7-12 years: 12.8-81.2 mcg/dL
- 13-17 years: 14.4-97.7 mcg/dL
- > or =18 years: 32.5-78.0 mcg/dL

**Clinical References:**

**Vitamin B12 and Folate, Serum**

**Clinical Information:** B12: Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states. Folate: The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate.(4) Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characteristically associated with macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions.(5) Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetra-hydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

**Useful For:** Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias Investigation of suspected folate deficiency

**Interpretation:** B12: Concentration of vitamin B12 <180 ng/L may cause megaloblastic anemia and/or peripheral neuropathies. Vitamin B12 concentrations <150 ng/L are considered evidence of vitamin B12 deficiency. Vitamin B12 concentrations between 150 ng/L and 300 ng/L are considered...
borderline. Follow-up testing for antibodies to intrinsic factor (IF) (IFBA / Intrinsic Factor Blocking Antibody, Serum) is recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies, follow-up testing of vitamin B12 tissue deficiency by measuring methylmalonic acid (MMA) (MMAS / Methylmalonic Acid [MMA], Quantitative, Serum) and/or homocysteine (HCYSP / Homocysteine, Total, Plasma) may be indicated if the patient is symptomatic. A normal serum concentration of vitamin B12 does not rule out tissue deficiency of vitamin B12. The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for MMA. If clinical symptoms suggest deficiency, measurement of MMA and homocysteine should be considered, even if serum vitamin B12 concentrations are normal. Folate: Serum folate is a relatively nonspecific test.(4) Low serum folate levels may be seen in the absence of deficiency and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results <4 mcg/L are suggestive of folate deficiency. The cut-off is based on consensus and was derived from the US NHANES III data.(5) Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Additional testing with homocysteine and MMA determinations may help distinguish between B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, both homocysteine levels and MMA levels are elevated. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:
VITAMIN B12
180-914 ng/L

FOLATE
> or =4.0 mcg/L
<4.0 mcg/L suggests folate deficiency

Clinical References:

Vitamin B12 Assay, Serum

Clinical Information: Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states.

Useful For: Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias

Interpretation: A serum vitamin B12 level less than 180 ng/L may cause megaloblastic anemia and peripheral neuropathies. Vitamin B12 levels less than 150 ng/L is considered evidence of vitamin B12 deficiency. Follow-up with a test for antibodies to intrinsic factor (IFBA / Intrinsic Factor Blocking
Antibody, Serum) is recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies and the patient is symptomatic, follow-up testing for vitamin B12 tissue deficiency may be indicated. Consider analysis of methylmalonic acid (MMAS / Methylmalonic Acid, Quantitative, Serum) and/or homocysteine (HCYS/ Homocysteine, Total, Plasma). Patients with serum vitamin B12 levels between 150 and 400 ng/L are considered borderline and should be evaluated further by functional tests for vitamin B12 deficiency. Plasma homocysteine measurement (HCYS/ Homocysteine, Total, Plasma) is a good screening test where a normal level effectively excludes vitamin B12 and folate deficiency in an asymptomatic patient. However, the test is not specific and many situations can cause an increased level. In contrast, an increased serum methylmalonic acid (MMAS / Methylmalonic Acid, Quantitative, Serum) level is more specific for cellular-level B12 deficiency and is not increased by folate deficiency. In patients being evaluated for vitamin B12 deficiency who have intrinsic factor blocking antibodies (IFBA), false elevations of vitamin B12 may occur due to IFBA interference, potentially obscuring a physiological deficiency of vitamin B12. If observed vitamin B12 concentrations are discordant with clinical presentation, measurement of methylmalonic acid (MMAS / Methylmalonic Acid, Quantitative, Serum) should be considered. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:
180-914 ng/L


**FVITB**

**57319**

**Vitamin B12 Binding Capacity**

Reference Values:
800 – 2600 pg/mL

Interpretive Information: Vitamin B12 Binding Capacity
This assay measures the unsaturated binding capacity of serum for Vitamin B12.

**FNIAC**

**91379**

**Vitamin B3 Niacin in Plasma**

Clinical Information: The amino acid tryptophan can be metabolically converted into niacin. Vitamin B3, also called niacin and nicotinic acid, is a water soluble B vitamin. It plays a role in releasing energy from carbohydrates and fats, metabolizes proteins, and assists in the production of some hormones and in the formation of red blood cells. Niacin is also thought to prevent and treat diabetes, improve circulation (as inositol hexaniacinate); and relieve arthritis. Niacin deficiency causes pellagra. Other forms of niacin may help prevent the development of childhood diabetes (Type I) in high risk children. The beneficial use of niacin (nicotinic acid, but not niacinamide) to prevent or treat elevated blood lipids and reduce cardiovascular disease risk is documented. Large amounts of niacin may result in "niacin intolerance" in 15-40% of people who try it and the unpleasant side effect of "skin-flushing" (similar to hot flashes). The RDA for niacin is only 13-18 mg. Vitamin B3 has been used orally and intravenously in connection with various health conditions including; high triglycerides, dysmenorrhea, hypothyroidism, and multiple sclerosis.
Reference Values:
Units: ug/mL
Adult Reference Range:
> or = 10 years
Normal  0.50 - 8.45
Low     <0.50
High    >8.45

Pediatric Reference Range:
<10 years
Normal  0.50 - 8.91
Low     <0.50
High    >8.91

FPAB
57394
Vitamin B5 (Pantothenic Acid) Bioassay
Reference Values:
Adult Reference Range
>10 Years                     37 - 147 ug/L

Pediatric Reference Range
<or = 1 Year                  3.45 to 825 ug/L
>1 year to 10 Years       3.45 to 229.2 ug/L

B6PRO
42360
Vitamin B6 Profile (Pyridoxal 5-Phosphate and Pyridoxic Acid), Plasma
Clinical Information: Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5'-phosphate esters. Due to its role as a cofactor in a number of enzymatic reactions, pyridoxal 5-phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present with chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid are observed in cases of hypophosphatasia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

Useful For: Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatasia
Interpretation: Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results: -If PLP is >100 mcg/L and PA is < or =30 mcg/L: -The increased PLP is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine) -If PLP is >100 mcg/L and PA is 31 to 100 mcg/L or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L: -The increased PLP is likely related to dietary supplementation; however a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is 51 to 80 mcg/L or PLP is >100 mcg/L and PA is >30 mcg/L or PLP is >100 mcg/L and PA is >100 mcg/L: -The elevated PLP is likely due to dietary supplementation.
FBIOT
91902

**Vitamin B7, H (Biotin)**

**Clinical Information:** Biotin, vitamin B7, or vitamin H, is a water soluble vitamin. The vitamin plays a role in the transferring of carbon dioxide in the metabolism of fat, carbohydrate and protein by functioning as an enzyme cofactor. It is involved in multiple biochemical reactions including niacin metabolism, amino acid degradation, and the formation of purine, which is an integral part of nucleic acids. It interacts with histone by the action of biotinyl-transferase. Sometimes the vitamin is used in weight reduction programs. It may be prescribed as a supplement for diabetic patients due to its role in carbohydrate metabolism. Biotin is commonly found in vitamin B complex and many food sources, such as milk, yeast, egg yolk, cereal, and mushrooms. The reference daily intake (RDI of 101.9(c) (8) IV]) for vitamin B7 is 300 micrograms. Deficiency in the vitamin may result in seborrheic dermatitis, alopecia, myalgia, hyperesthesia, and conjunctivitis. Disorders of biotin metabolism can be acquired or congenital. Biotinidase and holocarboxylase synthethase deficiency are the two better known forms of disorders. The lack of biotin-dependent pyruvate carboxylase, propionyl-CoA carboxylase, methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase can lead to the life-threatening disorder of multiple carboxylase deficiency. Treatment involves a daily dose of approximately 10 mg biotin/day. Irreversible mental or neurological abnormalities may result from delayed clinical intervention.

**Reference Values:**
- Pediatric <12 yrs: 100.0-2460.2 pg/mL
- Adults ≥12 yrs: 221.0-3004.0 pg/mL

VITE
42358

**Vitamin E, Serum**

**Clinical Information:** Vitamin E (alpha-tocopherol) contributes to the normal maintenance of biomembranes, the vascular and nervous systems, and provides antioxidant protection for vitamin A. The level of vitamin E in the plasma or serum after a 12- to 14-hour fast reflects the individual's reserve status. The current understanding of the specific actions of vitamin E is very incomplete. The tocopherols (vitamin E and related fat-soluble compounds) function as antioxidants and free-radical scavengers, protecting the integrity of unsaturated lipids in the biomembranes of all cells and preserving retinol (vitamin A) from oxidative destruction. Vitamin E is known to promote the formation of prostacyclin in endothelial cells and to inhibit the formation of thromboxanes in thrombocytes, thereby minimizing the aggregation of thrombocytes at the surface of the endothelium. Those influences on thrombocyte aggregation may be of significance in relation to risks for coronary atherosclerosis and thrombosis. Deficiency of vitamin E in children leads to reversible motor and sensory neuropathies; this problem also has been suspected in adults. Premature infants who require an oxygen-enriched atmosphere are at increased risk for bronchopulmonary dysplasia and retrolental fibroplasia; supplementation with vitamin E has been shown to lessen the severity of, and may even prevent, those problems. Deficiencies of vitamin E may arise from poor nutrition or from intestinal malabsorption. At-risk persons, especially children, include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia. Infantile cholangiopathies that may lead to malabsorption of vitamin E include intrahepatic and extrahepatic biliary atresia, paucity
of intrahepatic bile ducts, arteriohepatic dysplasia, and rubella-related embryopathy. In addition, low blood levels of vitamin E may be associated with abetalipoproteinemia, presumably as a result of a lack of the ability to form very low-density lipoproteins and chylomicrons in the intestinal absorptive cells of affected persons. Vitamin E toxicity has not been established clearly. Chronically excessive ingestion has been implicated as a cause of thrombophlebitis, although this has not been definitively verified.

**Useful For:** Evaluation of individuals with motor and sensory neuropathies Monitoring vitamin E status of premature infants requiring oxygenation Evaluation of persons with intestinal malabsorption of lipids

**Interpretation:**
- **Therapeutic Ranges:**
  - 0-17 years: 3.8-18.4 mg/L
  - > or =18 years: 5.5-17.0 mg/L

- **Significant deficiency:** <3.0 mg/L

**Reference Values:**
- 0-17 years: 3.8-18.4 mg/L
- > or =18 years: 5.5-17.0 mg/L

**Clinical References:**

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**VITK1**

**Vitamin K1, Serum**

**Clinical Information:** Vitamin K1 or phylloquinone is part of a group of similar fat soluble vitamins in which the 2-methyl-1,4-naphthoquinone ring is common. Phylloquinone is found in high amounts in leafy green vegetables and some fruits (avocado, kiwi). It is a required cofactor involved in the gamma-carboxylation of glutamate residues of several proteins. Most notably, the inactive forms of the coagulation factors prothrombin (factor II), factors VII, IX, and X and protein S and protein C are converted to their active forms by the transformation of glutamate residues to gamma-carboxyglutamic acid (Gla). Other proteins such as those involved in bone metabolism, cell growth, and apoptosis also undergo this Gla transformation. Measurement of vitamin K1 (phylloquinone) in fasting serum is a strong indicator of dietary intake and status.

**Useful For:** Assessment of circulating vitamin K1 concentration

**Interpretation:** Low vitamin K1 concentrations in the serum are indicative of insufficiency and poor vitamin K1 status.

**Reference Values:**
- > or =18 years: 0.10-2.20 ng/mL
- <18 years: not established

**Clinical References:**

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**VLTB**

**Volatile Screen, Blood**

**Clinical Information:** Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In
most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL.

**Useful For:** Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood. Quantification of the concentration of ethanol in blood that correlates with the degree of intoxication. Evaluation of toxicity to the measured volatile substances. This test is not intended for use in employment-related testing.

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

- **METHANOL**
  - Not detected (Positive results are quantitated.)
  - Toxic concentration: > or = 10 mg/dL

- **ETHANOL**
  - Not detected (Positive results are quantitated.)
  - Toxic concentration: > or = 400 mg/dL

- **ISOPROPANOL**
  - Not detected (Positive results are quantitated.)
  - Toxic concentration: > or = 10 mg/dL

- **ACETONE**
  - Not detected (Positive results are quantitated.)
  - Toxic concentration: > or = 10 mg/dL


**VLTBX 62745 Volatile Screen, Chain of Custody, Blood**

**Clinical Information:** Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL. Chain of custody is required whenever the results of testing could be used in a court of law. Chain of custody is a record of the disposition of a specimen to document the individuals that collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.
**Useful For:** Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood
Quantification of the concentration of ethanol in blood that correlates with the degree of intoxication
Evaluation of toxicity to the measured volatile substances Not intended for use in employment-related testing. Providing chain-of-custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

**ETHANOL**
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL

**ISOPROPANOL**
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

**ACETONE**
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL


**Volatile Screen, Chain of Custody, Random, Urine**

**Clinical Information:** Urine provides a medium for easy screening for methanol, ethanol, isopropanol, and acetone. Chain of custody is required whenever the results of testing could be used in a court of law. Chain of custody is a record of the disposition of a specimen to document the individuals that collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with subsequent quantitation Providing chain of custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can
be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

**ETHANOL**
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

**ISOPROPANOL**
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

**ACETONE**
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL


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**VLTU**

**8826**

**Volatile Screen, Random, Urine**

**Clinical Information:** Urine provides a medium for easy screening for methanol, ethanol, isopropanol, and acetone.

**Useful For:** Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with subsequent quantitation

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
ETHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

ISOPROPANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ACETONE
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL


Volatile Screen, Serum

Clinical Information: Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Methanol and isopropanol are highly toxic; toxicity results from ingestion (exogenous). Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis (endogenous). It also is a metabolite of isopropanol. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. On average, the serum or plasma concentration of the alcohols is 1.2-fold higher than blood concentration. For example, the serum or plasma would contain approximately 0.10 g/dL of ethanol in a blood specimen that contains 0.08 g/dL ethanol. Due to potential variations in the serum to whole blood ratio, serum should not be used in a medico-legal context. However, in the context of medical/clinical assessment, serum or plasma may be submitted for analysis.

Useful For: Detection and quantitation of acetone, methanol, isopropanol, and ethanol in serum. Quantification of the concentration of ethanol in serum correlates with degree of intoxication. Evaluation of toxicity to the measured volatile substances

Interpretation: Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

Reference Values:

METHANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

ETHANOL
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL
**ISOPROPANOL**  
Not detected (Positive results are quantitated.)  
Toxic concentration: > or =10 mg/dL

**ACETONE**  
Not detected (Positive results are quantitated.)  
Toxic concentration: > or =10 mg/dL

**Clinical References:**  

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**VWD8B**  
**von Willebrand Disease 2N (Subtype Normandy), Plasma**

**Clinical Information:**  
von Willebrand disease (VWD) is a bleeding disorder due to quantitative or qualitative defects in von Willebrand factor (VWF), which results from pathogenic alterations in the VWF gene. VWD constitutes 1 of the 2 most common bleeding disorders. Most subtypes of VWD are inherited as autosomal dominant traits, although autosomal recessive variants occur. In hemostasis, there are 2 essential roles for VWF. The first is its ability to promote platelet adhesion to damaged vessel walls, and the second is to function as a carrier protein for Factor VIII (FVIII). Thus, noncovalent binding of FVIII to VWF is necessary for normal survival of FVIII in the blood circulation. In patients with severe VWD the circulating half-life of endogenous or infused FVIII is shorter than expected. Pathogenic alterations within the FVIII binding domain of VWF may result in an isolated αć-deficiencyαĐ of FVIII associated with a clinically mild to moderate bleeding disorder which may be misdiagnosed as Hemophilia A (HA). Abnormal binding of FVIII to VWF can be detected with a binding assay. Since its initial description in patients from the Normandy region of France, more recent studies suggest that VWD type 2N or Normandy (VWD2N) has been associated with a more severe phenotype among patients who are homozygous for pathogenic alterations within the FVIII binding domain of VWF. In an international survey, FVIII binding defect was detected in 58/1198 (4.8%) of patients with mild HA. Other studies confirm these findings and reveal that 1.5% to 16.6% of patients with VWD Type 1 have the FVIII binding defect. The diagnosis of VWD2N has 2 main implications: 1) genetic counseling differs considerably from that for X-linked recessive HA since the inheritance of VWD2N is autosomal recessive; and 2) optimal treatment or prophylaxis of bleeding requires factor replacement therapy with products containing functional VWF.

**Useful For:**  
Diagnosis of von Willebrand disease (VWD) type 2N Evaluation of patients diagnosed with mild-to-moderate hemophilia A with an autosomal inheritance pattern Evaluation of hemophilia A patients with a shortened survival of infused factor VIII (FVIII) (not caused by a specific FVIII inhibitor) Evaluation of female patients with low FVIII activity and no prior family history of hemophilia A Evaluation of patients with Type 1 or Types 2A, 2B, or 2M VWD with FVIII activity discordantly-lower than the von Willebrand factor antigen level

**Interpretation:**  
A reduced capacity of patientαĐ von Willebrand factor (VWF) to bind to recombinant factor VIII (FVIII) is consistent with von Willebrand disease (VWD) type 2N (Normandy). A mild to moderate decrease of the VWF:FVIIIIB ratio suggests the presence of a VWD Type 2N due to heterozygous variants in the FVIII binding domain of VWF. If clinically indicated, DNA sequence analysis of the FVIII binding domain of VWF may provide useful information. Results do not exclude other variants of congenital VWD, eg, type 1, 2A, 2B or 2M or congenital hemophilia A. Clinical correlation should be made between patient and family bleeding history and results of VWF antigen, factor VIII and VWF activity assays.

**Reference Values:**  
68-106%
Pediatric reference ranges have not been established for this assay but likely achieve adult reference range by 18 years of age.

**Clinical References:**

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**von Willebrand Disease Profile Interpretation**

**Clinical Information:** von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma. VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic "plug" and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor. VWF circulates in the blood in 2 distinct compartments. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high-molecular-weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory with the VWF activity assay, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers and is useful as a reflexive test for subtyping von Willebrand disease (VWD). Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within each individual over time and also with blood type (normal type "O" individuals may have VWF lower than normals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. VWF antigen measurement assesses the mass of plasma VWF protein, but does not reflect VWF functions or platelet VWF. The function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal, including epistaxis, menorrhagia, gastrointestinal bleeding, and ease of bruising, but surgical or posttraumatic bleeding can also occur. Subtypes of inherited VWD are: Type 1 VWD: VWF plasma levels (antigen and activity) typically are both concordantly reduced in type 1 VWD. Because of this reduction, the level of coagulation factor VIII is often secondarily reduced also. Type 1 VWD is the most common VWD variation, representing 70% to 80% of clinical VWD. It is typically inherited in autosomal dominance fashion, although recessively inherited VWD also occurs (eg, type 3 VWD). Clinical severity ranges from mild or minimal to a moderately severe bleeding diathesis, and tends to correlate most closely with VWF activity. Severe type 1 disease is also called type 3 VWD, but the distinction between the 2 may sometimes be difficult. Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of types 2A and 2B, but are normal in type 2M or 2N. VWF activity is decreased in types 2A, 2B, and 2M, and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (typically 5%-30% of mean normal), with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomally inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A).
Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen not due to loss of HMW multimers. One variant of type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Type 3 VWD: VWF is absent or markedly decreased in type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal, with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected. Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.

**Useful For:** Detection of deficiency or abnormality of von Willebrand factor (VWF) and related deficiency of factor VIII coagulant activity

**Subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare)** This test is not useful for detection of hemophilia carriers. This test is not useful for differentiating type 2A versus 2B VWD or platelet-type VWD (pseudo-VWD).

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**
Only orderable as part of a profile. For more information see AVWPR / von Willebrand Disease Profile, Plasma.

An interpretive report will be provided.

**Clinical References:**

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**von Willebrand Disease Profile Technical Interpretation**

**Clinical Information:** von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma. VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic "plug" and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor. VWF circulates in the blood in 2 distinct compartments. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high-molecular-weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory with the VWF activity assay, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers and is useful as a reflexive test for subtyping von Willebrand disease (VWD). Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within each individual over time and also with blood type (normal type "O" individuals may have VWF lower than normals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. VWF antigen measurement assesses the
mass of plasma VWF protein, but does not reflect VWF functions or platelet VWF. The function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal, including epistaxis, menorrhagia, gastrointestinal bleeding, and ease of bruising, but surgical or posttraumatic bleeding can also occur. Subtypes of inherited VWD are:

Type 1 VWD: VWF plasma levels (antigen and activity) typically are both concordantly reduced in type 1 VWD. Because of this reduction, the level of coagulation factor VIII is often secondarily reduced also. Type 1 VWD is the most common VWD variation, representing 70% to 80% of clinical VWD. It is typically inherited in autosomal dominance fashion, although recessively inherited VWD also occurs (eg, type 3 VWD). Clinical severity ranges from mild to moderate to a moderately severe bleeding diathesis, and tends to correlate most closely with VWF activity. Severe type 1 disease is also called type 3 VWD, but the distinction between the two may sometimes be difficult. Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of types 2A and 2B, but are normal in type 2M or 2N. VWF activity is decreased in types 2A, 2B, and 2M, and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (typically 5%-30% of mean normal), with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomally inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A). Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen due to loss of HMW multimers. One variant of type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Type 3 VWD: VWF is absent or markedly decreased in type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal), with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected. Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.

Useful For: Detection of deficiency or abnormality of von Willebrand factor (VWF) and related deficiency of factor VIII coagulant activity Subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare) This test is not useful for detection of hemophilia carriers. This test is not useful for differentiating type 2A versus 2B VWD or platelet-type VWD (pseudo-VWD).

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as part of a profile. For more information see AVWPR / von Willebrand Disease Profile, Plasma.

An interpretive report will be provided.


von Willebrand Disease Profile, Plasma
603550
Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 2596
Clinical Information: von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma. Â VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic “plug” and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor. Â VWF circulates in the blood in 2 distinct compartments. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. Â Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high-molecular-weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory with the VWF activity assay, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers and is useful as a reflexive test for subtyping von Willebrand disease (VWD). Â Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within each individual over time and also with blood type (normal type “O” individuals may have VWF lower than normal individuals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. Â VWF antigen measurement assesses the mass of plasma VWF protein, but does not reflect VWF functions or platelet VWF. The function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. Â VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal, including epistaxis, menorrhagia, gastrointestinal bleeding, and ease of bruising, but surgical or posttraumatic bleeding can also occur. Â Subtypes of inherited VWD are: Â Type 1 VWD: VWF plasma levels (antigen and activity) typically are both concordantly reduced in type 1 VWD. Because of this reduction, the level of coagulation factor VIII is often secondarily reduced also. Type 1 VWD is the most common VWD variation, representing 70% to 80% of clinical VWD. It is typically inherited in autosomal dominance fashion, although recessively inherited VWD also occurs (eg, type 3 VWD). Clinical severity ranges from mild or minimal to a moderately severe bleeding diathesis, and tends to correlate most closely with VWF activity. Severe type 1 disease is also called type 3 VWD, but the distinction between the two may sometimes be difficult. Â Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of types 2A and 2B, but are normal in type 2M or 2N. Â VWF activity is decreased in types 2A, 2B, and 2M, and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (typically 5%-30% of mean normal), with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomal inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A). Â Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen not due to loss of HMW multimers. One variant of type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Â Type 3 VWD: VWF is absent or markedly decreased in type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal, with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Â Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected. Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.
Useful For: Detection of deficiency or abnormality of von Willebrand factor (VWF) and related deficiency of factor VIII coagulant activity. Subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare). This test is not useful for detection of hemophilia carriers.

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values: An interpretive report will be provided.


VWFNG von Willebrand Disease, VWF Gene, Next-Generation Sequencing, Varies

Clinical Information: von Willebrand disease (VWD) is a bleeding diathesis that usually involves mucous membranes and skin sites. It is typically of mild to moderate severity, although life-threatening bleeding in the central nervous system or gastrointestinal (GI) tract can occur. The most common presenting symptoms in individuals affected by VWD include epistaxis, menorrhagia, bleeding after dental extraction, postoperative bleeding, ecchymoses, bleeding from minor cuts or abrasions, gingival bleeding, and hemarthrosis.(1) VWD affects up to 1% of the general population. While VWD occurs with equal frequency among men and women, symptoms in women are more obvious because of increased bleeding during menstrual periods, pregnancy, and after childbirth. VWD is a result of defects in the concentration, structure, or function of von Willebrand factor (VWF), leading to decreased factor VIII (FVIII) in circulation and/or impaired platelet adhesion and aggregation at the site of vascular injury. The VWF gene encodes for VWF, a protein that protects blood clotting FVIII from degradation in circulation and promotes platelet adhesion and aggregation at the site of vascular injury. In circulation, VWF assembles into linear strings called multimers, the size of which is biologically important, larger multimers being more reactive than smaller multimers. In general, bleeding risk is typically proportional to severity of VWF deficiency or the degree to which it impairs VWF function. However, bleeding risk is highly variable in von Willebrand due to the complexity of the protein structure and function and the great heterogeneity in alteration types that cause this disease. Further, because VWD is an autosomal gene, biallelic combinations of different sequence variants also contribute to phenotypic variability. VWD is classified into 3 types: Type 1- Partial quantitative deficiency of VWF Type 2- Qualitative VWF defects including -Type 2A- Decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight VWF multimers, -Type 2B- Increased affinity for platelet glycoprotein Ib -Type 2M- Decreased VWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight VWF multimers -Type 2N- Markedly decreased binding affinity for factor VIII Type 3- Virtually complete deficiency of VWF VWD type 1 and type 2B are inherited in an autosomal dominant manner. VWD type 2A and 2M have been observed to be inherited in both autosomal dominant or autosomal recessive manners. VWD type 2N and 3 are inherited in an autosomal recessive manner. Causes of acquired (nongenetic) VWD that should be excluded prior to genetic testing include: 1) Autoimmune clearance of inhibition of VWF, typically in association with lymphoproliferative diseases, monoclonal gammopathies, systemic lupus erythematosus, and some cancers 2) Increased shear-induced proteolysis of VWF, which can occur with cardiovascular lesions or with pulmonary hypertension 3) Increased binding of VWF to platelets and other cell surfaces, associated with myeloproliferative disorders 4) Nonimmune-related hypothyroidism 5) Use of valproic acid, ciprofloxacin, griseofulvin, hydroxyethyl starch, and other drugs.

Useful For: Genetic confirmation of hereditary von Willebrand disease with the identification of alterations in the VWF gene known or suspected to cause the condition. Testing for close family members of an individual with a von Willebrand disease diagnosis.

Interpretation: An interpretive report will be provided. Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics
(ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Reference Values:
An interpretive report will be provided.

Clinical References:

VWACT von Willebrand Factor Activity, Plasma

Clinical Information:
von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments, plasma VWF and platelet VWF. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein, but does not measure platelet VWF protein. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. Patients with congenital severe type 3 von Willebrand disease (VWD) have markedly decreased or immeasurably low VWF antigen in the plasma (and in the platelets), and plasma VWF activity is very low or not detectable. Patients with types 2A and 2B variants of VWD (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen, but typically have decreased plasma VWF activity, and decreased higher molecular weight VWF multimers in the plasma. Patients with type 2M or type 2N VWD have normal levels of antigen, but either decreased VWF activity not caused by absence of higher molecular weight VWF multimers (type 2M VWD), or decreased factor VIII coagulant activity (type 2N VWD). Patients with type 1 VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and activity. Patients with acquired von Willebrand syndrome (AVWS) may have either normal or decreased plasma VWF antigen, and decreased VWF activity. Note: This activity assay is most effective when it is combined with measurement of von Willebrand factor: VWF antigen and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting (eg, AVWPR / von Willebrand Profile, Plasma).

Useful For:
Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtypes or differentiation of VWD from hemophilia A Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or VWF concentrates in patients with VWD

Interpretation: von Willebrand factor (VWF) activity is reduced in parallel with VWF antigen in von Willebrand disease (VWD), except in types 2A, 2B, and 2M, and some cases of acquired von Willebrand syndrome (AVWS) in which the VWF activity is disproportionately decreased relative to the level of VWF antigen. The VWF activity may be decreased in congenital VWD or AVWS that may be associated with a variety of disorders including monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, hypothyroidism, severe aortic stenosis, left ventricular assist device, and arteriovenous malformation. The VWF activity may be increased in association with pregnancy or estrogen use (including oral contraceptives), acute (“acute-phase reactant”) or chronic inflammation, exercise or stress, liver disease, vasculitis, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Such increases in VWF activity may obscure the laboratory diagnosis of mild VWD.Â

Reference Values:
Normal, full-term newborn infants may have mildly increased levels which reach adult levels by 90 days postnatal. Healthy, premature infants (30-36 weeks gestation) may have increased levels that reach adult levels by 180 days.

Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) activity than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF activity as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.


von Willebrand Factor Antigen, Plasma

Clinical Information: The von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments; plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells, and platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein but does not reflect VWF functions or platelet VWF. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma ristocetin cofactor activity. Decreased VWF antigen may be seen in: -Congenital von Willebrand disease -Acquired von Willebrand disease (AVWD) that may be associated with monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, and hypothyroidism. Increased VWF antigen may be seen in association with: -Pregnancy and/or estrogen use -Inflammation (acute-phase reactant) -Exercise or stress -Liver disease -Vasculitis -Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Useful For: Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtype (in conjunction with von Willebrand factor ristocetin cofactor activity and factor VIII coagulant activity) Differentiation of VWD from hemophilia A (in conjunction with factor VIII coagulant assay) Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or von Willebrand factor (VWF) concentrates in patients with VWD

Interpretation: Patients with congenital severe type III von Willebrand disease (VWD) have a markedly decreased or undetectable level of von Willebrand factor (VWF) antigen in the plasma (and in the platelets), in addition to a plasma ristocetin cofactor activity that is very low or not detectable. Patients with types IIA and IIB variants of VWF (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen. However, they typically have decreased plasma ristocetin cofactor activity, along with decreased higher molecular-weight VWF multimers in the plasma. Patients with types IIM or IIN VWD have normal levels of VWF antigen. In spite of this, they either have decreased vWF ristocetin cofactor activity, not caused by absence of higher molecular weight VWF multimers (type IIM VWD), or decreased factor VIII coagulant activity (type IIN VWD). Patients with type I VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen.
VWF antigen and ristocetin cofactor activity. Patients with acquired VWD may have either normal or decreased plasma VWF antigen.

Reference Values:
55-200%

Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) antigen than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF antigen as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.

Children: Neonates, infants, and children have normal or mildly increased plasma VWF antigen, with respect to the adult reference range.

Clinical References:

Von Willebrand Factor Multimer Analysis, Plasma

Clinical Information: von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that has essential roles in primary hemostasis. Wild-type VWF molecules are series of multimers varying in size from dimers to multimers over 40 subunits (>10-million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury, and are the most hemostatically active form of VWF. The biological functions of VWF are as follows: 1. VWF is a ligand and mediates platelet adhesion to the subendothelial collagen at the site of vessel wall injury by binding to the platelet receptor glycoprotein (GP)-Ib, V, IX complex and subendothelial collagen. 2. VWF binds and stabilizes procoagulant factor VIII in the circulation. 3. Under conditions of high shear, VWF also mediates platelet-platelet cohesion by binding to the platelet receptor GP-IIb/IIIa (integrin alpha IIb beta3) von Willebrand disease (VWD) is the most common hereditary bleeding disorder that is caused by quantitative or qualitative VWF defect. VWD manifests clinically as easy bruising, mucocutaneous bleeding (eg, epistaxis, menorrhagia), and bleeding after trauma or surgery. VWD has been classified into 3 major types: -Type 1, typically an autosomal dominant disease, is the most common, accounting for approximately 70% of VWD patients. It represents a quantitative deficiency of VWF of variable severity. -Type 2, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of VWF. Four subtypes have been identified: 2A, 2B, 2M, and 2N. -Type 3, an autosomal recessive disorder, leads to severe disease with virtually undetectable levels of VWF, as well as very low levels of factor VIII. Acquired von Willebrand syndrome (AVWS) is associated with a number of different disease states and is caused by several different pathophysiological mechanisms, including antibody formation, proteolysis, binding to tumor cells with increased clearance, and decreased synthesis. AVWS is most frequently described in patients with dysproteinemias (including monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma, and macroglobulinemia), lymphoproliferative disorders, myeloproliferative disorders (eg, essential thrombocythemia), autoimmune diseases (eg, systemic lupus erythematosus), high-shear stress cardiovascular conditions such as severe aortic stenosis, gastrointestinal angiodyplasia, and hypothyroidism.

Useful For: As a reflex component of several coagulation consultation unit codes, when indicated When results of complementary laboratory tests are abnormally low or discordant (eg, F8A / Coagulation Factor VIII Activity Assay, Plasma; VWACT / von Willebrand Factor Activity, Plasma; and VWAG / von Willebrand Factor Antigen, Plasma) To subtype von Willebrand disease (VWD) (primarily identify variants of type 2 VWD) As an aid in determining appropriate treatment

Interpretation: The plasma von Willebrand factor (VWF) multimer analysis is a qualitative visual
assessment of the size spectrum and the banding pattern of vWF multimers. This test is used to identify variants of type 2 von Willebrand disease (VWD) that have fewer of the largest multimers, have unusually large multimers, or have qualitatively abnormal "bands" that indicate an abnormal vWF structure.

**Reference Values:**
Only orderable as part of a coagulation reflex. For more information see:
- ALUPP / Lupus Anticoagulant Profile, Plasma
- ALBLD / Bleeding Diathesis Profile, Limited, Plasma
- AVWPR / von Willebrand Disease Profile, Plasma

An interpretive report will be provided.

**Clinical References:**

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**VWFMS**

**von Willebrand Factor Multimer Analysis, Plasma**

**Clinical Information:** von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that has essential roles in primary hemostasis. Wild-type VWF molecules are series of multimers varying in size from dimers to multimers over 40 subunits (>10 million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury, and are the most hemostatically active form of VWF. The biological functions of VWF are as follows:
- VWF is a ligand and mediates platelet adhesion to the subendothelial collagen at the site of vessel wall injury by binding to the platelet receptor glycoprotein (GP)-Ib, V, IX complex, and subendothelial collagen 2. VWF binds and stabilizes procoagulant factor VIII in the circulation 3. Under conditions of high shear, VWF also mediates platelet-platelet cohesion by binding to the platelet receptor GP-IIIa (integrin alpha IIb beta3) to promote platelet aggregation and thrombus formation.
- VWD has been classified into 3 major types: -Type 1, typically an autosomal dominant disease, is the most common, accounting for approximately 70% of VWD patients. It represents a quantitative deficiency of VWF of variable severity. -Type 2, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of VWF. Four subtypes have been identified: 2A, 2B, 2M, and 2N. -Type 3, an autosomal recessive disorder, leads to severe disease with virtually undetectable levels of VWF, as well as very low levels of factor VIII. Acquired von Willebrand syndrome (AVWS) is associated with a number of different disease states and is caused by several different pathophysiological mechanisms, including antibody formation, proteolysis, binding to tumor cells with increased clearance, and decreased synthesis. AVWS is most frequently described in patients with dysproteinemias (including monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma, and macroglobulinemia), lymphoproliferative disorders, myeloproliferative disorders (eg, essential thrombocythemia), autoimmune diseases (eg, systemic lupus erythematosus), high-shear stress cardiovascular conditions such as severe aortic stenosis, gastrointestinal angiodysplasia, and hypothyroidism.

**Useful For:** Resolving discrepancies when results of complementary laboratory tests (eg, F8A / Coagulation Factor VIII Activity Assay, Plasma; VWACT / von Willebrand Factor Activity, Plasma; and VWAG / von Willebrand Factor Antigen, Plasma) are abnormally low or discordant Subtyping von Willebrand disease (VWD) (primarily identify variants of type 2 VWD) Aiding in determining appropriate treatment Identifying variants of type 2 VWD that have fewer of the largest multimers, have
unusually large multimers, or have qualitatively abnormal "bands" that indicate an abnormal von Willebrand factor structure

**Interpretation:** The plasma von Willebrand factor (VWF) multimer analysis is a qualitative visual assessment of the size spectrum and the banding pattern of VWF multimers.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Voriconazole, Serum**

**Clinical Information:** Voriconazole (Vfend) is an antifungal agent approved for treatment of invasive aspergillosis and candidemia/candidiasis, as well as for salvage therapy for infections in patients refractory to or intolerant of other antifungal therapy. The drug inhibits the fungal enzyme 14a-sterol demethylase, a critical step in ergosterol biosynthesis. Voriconazole is metabolized in the liver primarily by cytochrome P450 (CYP) 2C19; CYP2C9, and CYP3A4 play limited roles. The primary metabolite is voriconazole N-oxide, which has no antifungal activity. Drug clearance is primarily dependent on hepatic metabolism. The pharmacokinetics of voriconazole is highly variable and nonlinear, which results in an increased dose leading to a greater than proportional increase in serum concentration. The bioavailability of oral voriconazole is greater than 95%. Approximately 60% of the drug in serum is protein bound. Voriconazole has a volume of distribution of 4.6 L/kg. Most (80%) of the drug is excreted in the urine, exclusively as metabolites. Adverse effects of voriconazole include visual disturbances, skin rashes, and elevated liver enzyme levels.

**Useful For:** Monitoring trough levels of voriconazole is suggested in individuals with reduced liver function, individuals with cytochrome P450 (CYP) 2C19 alterations associated with poor metabolic function, patients taking other medications that affect CYP2C19 activity, and in patients experiencing potential toxicity Monitoring trough levels may be reasonable in patients who are not responding optimally or have drug interactions that may decrease voriconazole levels, or to ensure adequate oral absorption

**Interpretation:** Trough levels above 6 mcg/mL (and especially >10 mcg/mL) have been associated with toxicity in several reports. Trough levels below 1 mcg/mL have been associated with suboptimal response in several reports.

**Reference Values:**
1.0-5.5 mcg/mL

Trough level (ie, immediately before next dose) monitoring is recommended.

**Clinical References:**
Wall Eyed Pike (Sander vitreus)(Stizostedium vitreum) IgE

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**
<0.35 kU/L

Walnut Component rJug r 1

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.10 kU/L

Walnut Component rJug r 3

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.10 kU/L

Walnut Food (Juglans spp) IgG

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Walnut Tree, IgE, Serum

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to walnut tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>3 3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*


**WARSQ**

**Warfarin Response Genotype, Varies**

**Clinical Information:** Warfarin is a Coumarin-based drug commonly utilized in anticoagulation therapy to prevent thrombosis due to inherited and acquired hemostatic disorders. The drug is also used in a number of other medical conditions and treatments including atrial fibrillation and hip replacement surgery. Warfarin acts by interfering with the metabolism of vitamin K, which is necessary for production of key coagulation factors. Warfarin inhibits vitamin K recycling by blocking its metabolism at the vitamin K-epoxide intermediate; thereby decreasing the amount of available vitamin K. Warfarin has a narrow therapeutic window; undermedicating increases the risk for thrombosis and overmedicating increases the risk for cerebrovascular accidents. Warfarin therapy has one of the highest rates of severe adverse drug reactions. Warfarin is dosed using nongenetic factors including gender, weight, and age, and is monitored by coagulation testing in order to maintain the international normalized ratio (INR) within specific limits. However, warfarin metabolism is highly variable and dependent upon genetic factors. Variants within 3 genes and 1 intragenic locus are known to affect the metabolism of warfarin and the dose needed to maintain the correct serum drug level and degree of anticoagulation. The CYP2C9 gene encodes the cytochrome P450 (CYP) 2C9 enzyme that primarily metabolizes the more active isomer of warfarin (S-warfarin) to inactive products. Some CYP2C9 variants result in decreased enzymatic activity and may lead to increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. The second gene, VKORC1 encodes vitamin K epoxide reductase complex subunit-1, a small transmembrane protein of the endoplasmic reticulum that is part of the vitamin K cycle and the target of warfarin therapy. Vitamin K epoxide, a by-product of the carboxylation of blood coagulation factors, is reduced to vitamin K by VKORC1. A VKORC1 promoter variant leads to decreased expression of the gene, resulting in reduced availability of vitamin K. This may cause increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. In addition, there are variations in VKORC1 that lead to warfarin resistance that are tested by this assay. These variations are rare. CYP4F2 metabolizes reduced vitamin K to hydroxyl-vitamin K1, thus removing it from the pathways involved in the activation of clotting factors impacted by warfarin. In individuals who self-identify as being of non-African ancestry, carriers of the CYP4F2*3 (C.1297G>A; rs2108622) variant may need a small (5%-10%) warfarin dosage increase to achieve therapeutic goals. The rs12777823G>A variant is located intragenic in the CYP2C locus on chromosome 10. The A allele has been associated with the need for a 10% to 15% decrease in dose in individuals who self-identify as being of African ancestry. CYP2C9: CYP2C9 metabolizes a wide variety of drugs including warfarin and phenytoin. (Note that if testing is desired for other CYP2C9 substrates, order 2C9QT / Cytochrome P450 2C9 Genotype, Varies. A number of specific CYP2C9 variants result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in this assay and their effect on the activity of the enzyme (Table 1): Table 1: CYP2C9 allele cDNA nucleotide change (NM_000771.3) Effect on enzyme metabolism *1 None (wild type) Normal activity *2 c.430C>T Reduced activity *3 c.1075A>C No activity *4 c.1076T>C Reduced activity *5 c.1080C>G Reduced activity *6 c.818delA No activity *8 c.449G>A Reduced activity *9 c.752A>G Normal activity *11 c.1003C>T Reduced activity *12
c.1465C>T Reduced activity *13 c.269C>T No activity *14 c.374G>A Reduced activity *15 c.485C>A No activity *16 c.895A>G Reduced activity *17 c.1144C>T Reduced activity *18 c.1190A>C No activity *25 c.353_362del No activity *26 c.389C>G Reduced activity *28 c.641A>T Reduced activity *30 c.1429G>A Reduced activity *33 c.395G>A No activity *35 c.374G>T:c.430C>T No activity VKORC1: The c.-1639 promoter variant is located in the second nucleotide of an E-Box (CANNTG), and its presence disrupts the consensus sequence, reducing promoter activity. In vitro experiments show a 44% higher transcription level of the G versus the A allele.(1) The c.-1639G>A nucleotide change results in decreased gene expression and reduced enzyme activity. This test also determines the genotype for multiple other loci within VKORC1 that have been associated with warfarin resistance. The mechanism by which these variations cause warfarin resistance is not clearly understood. Table 2: Additional Variants Tested Gene/SNV cDNA nucleotide change (VKORC1 NM_024006.5; CYP4F2 NM_001082.4) Effect on enzyme metabolism VKORC1 c.-1639G>A Warfarin sensitivity VKORC1 c.85G>T Warfarin resistance VKORC1 c.106G>T Warfarin resistance VKORC1 c.121G>T Warfarin resistance VKORC1 c.134T>C Warfarin resistance VKORC1 c.172A>G Warfarin resistance VKORC1 c.196G>A Warfarin resistance VKORC1 c.358C>T Warfarin resistance VKORC1 c.383T>G Warfarin resistance CYP4F2*3 c.1297G>A Warfarin resistance rs12777823G>A* N/A Warfarin sensitivity * rs12777823G>A is an intergenic single nucleotide variant (SNV) Warfarin dosing may require adjustment depending on the genotypes identified and the predicted phenotype. Patients who have high warfarin sensitivity may benefit from greatly reduced warfarin dosage or by transitioning to another comparable medication.(2) Similarly, in rare instances, individuals with VKORC1 warfarin resistance variants, may require a higher warfarin dose or may benefit from selection of an alternate medication. Useful For: Identifying patients who may require warfarin dosing adjustments(3,4) including:

FWARP 75517

**Warfarin, Plasma**

**Reference Values:**

0.2 mcg/mL

The reported value may vary based on dilution or weight of the specimen.

WSPV 82659

**Wasp Venom, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to wasp venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's
**Watermelon IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Watermelon, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergy to watermelon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**WEED1**

**Weed Panel # 1, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to English plantain, lamb's quarters, mugwort, Russian thistle, and short ragweed allergen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: Responsible for allergic disease and/or anaphylactic episode To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
</table>

Reference values apply to all ages.


**WEED2**

**Weed Panel # 2, Serum**

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to English plantain, lamb's quarters, mugwort, scale, and Western ragweed allergen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Reference Values:

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Reference values apply to all ages.


Weed Panel # 3, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to English plantain, lamb's quarters, red sorrel, and Russian thistle allergen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with
immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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**WEED4 81885**

**Weed Panel # 4, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to giant ragweed, short ragweed, and Western ragweed. A listing of allergens is provided below. Defining the allergen responsible for eliciting signs and symptoms Identifying allergies: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy. Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

**Interpretation:** Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

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<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:


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### West Nile CSF Interpretation

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the CDC, among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid. Aids in diagnosis of central nervous system infection with West Nile virus

**Interpretation:** IgM: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested. IgG: A positive result may indicate recent or past central nervous system (CNS) infection with WNV. Clinical correlation is necessary. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

### Reference Values:

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
West Nile Serum Interpretation

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe. (1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death. (2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. (1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Laboratory diagnosis of infection with West Nile virus

Interpretation: IgG: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (eg, before 8 to 10 days post-infection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

Reference Values:
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.


Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
West Nile Virus Antibody, IgG and IgM, Serum

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) In 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) tests (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Laboratory diagnosis of infection with West Nile virus in serum specimens

Interpretation: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days postinfection to demonstrate rising IgG antibody levels between the 2 serum specimens. Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens collected too early in the acute phase (eg, before 8 to 10 days postinfection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen collected approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

Reference Values:
IgG: negative
IgM: negative
Reference values apply to all ages

Clinical References:
**West Nile Virus Antibody, IgG and IgM, Spinal Fluid**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe. In 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2873 (51%) were classified as neuroinvasive disease (e.g., meningitis or encephalitis) and 286 (5%) cases resulted in death. Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.

Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) (LCWNV / West Nile Virus, Molecular Detection, PCR, Spinal Fluid) can detect WNV RNA in specimens from patients with recent WNV infection (i.e., 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Aiding in diagnosis of central nervous system infection with West Nile virus

**Interpretation:** Presence of specific IgM-class antibodies to West Nile virus (WNV) is consistent with the acute phase of WNV meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum. The absence of IgM antibodies to WNV may indicate absence of disease. However, specimens collected too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested. The presence of IgG-class antibodies to WNV may indicate recent or past central nervous system (CNS) infection with WNV. Clinical correlation is necessary. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**
- IgG: Negative
- IgM: Negative

**Reference values apply to all ages.**

**Clinical References:**

**West Nile Virus Antibody, IgG, Serum**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in...
Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Laboratory diagnosis of infection with West Nile virus

**Interpretation:** IgG: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (eg, before 8 to 10 days post-infection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

**Reference Values:**
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

**Clinical References:**

**WNNGC 36774 West Nile Virus Antibody, IgG, Spinal Fluid**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the CDC, among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most
important risk factor for death, and patients older than 70 years of age are at particularly high risk. (1)
Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in
serum specimens. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can detect WNV RNA
in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific
antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the
sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in
blood, from patients with known WNV infection.

**Useful For:** Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM,
Spinal Fluid. Aids in diagnosis of central nervous system infection with West Nile virus

**Interpretation:** A positive result may indicate recent or past central nervous system (CNS) infection
with West Nile virus (WNV). Clinical correlation is necessary. This assay is unable to distinguish
between intrathecal antibody synthesis and serum antibodies introduced into the cerebrospinal fluid at the
time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be
interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**
Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

**Clinical References:**
Intern Med 2002;137:173-179
2. MMWR: West Nile Virus and Other Arboviral Diseases—United States,
3. Brinton MA: The molecular biology of West Nile Virus: a new invader of
4. Centers for Disease Control and
Prevention (CDC). Provisional Surveillance Summary of the West Nile Virus epidemic. United States,
5. Centers for Disease
Control and Prevention (CDC). Investigations of West Nile Virus infections in recipients of blood
transfusions. MMWR Morb Mortal Wkly Rep 2002;51(43):973-974
acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (eg, before 8 to 10 days post-infection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14 days post-infection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

Reference Values:
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

Clinical References:

West Nile Virus Antibody, IgM, Spinal Fluid

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe. Most recently, in 2012, a total of 5,674 cases of WNV were reported to the CDC, among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningoencephalitis) and 286 (5%) cases resulted in death. Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid. Aid in diagnosis of central nervous system infection with West Nile virus

Interpretation: A positive result is consistent with the acute phase of West Nile virus (WNV) meningoencephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested.

Reference Values:
Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

West Nile Virus, RNA, PCR, Molecular Detection, Blood

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans.(1,2,3) Until the virus infection was recognized in 1999 in birds in New York City, WNV had been detected only in the Eastern hemisphere with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms including headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningoencephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can also be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources.(5) Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

**Useful For:** Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset) Blood may provide greater sensitivity for polymerase chain reaction detection of WNV RNA than other sources. This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

**Interpretation:** A positive result indicates the presence of West Nile virus (WNV) RNA and is consistent with early WNV infection.

**Reference Values:**
Negative

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans (1, 2, 3). Until the virus infection was recognized in 1999 in birds in New York City, WNV had been detected only in the Eastern hemisphere with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms including headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can also be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing. However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources. Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

Useful For: Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) using serum specimens. An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset). This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

Interpretation: A positive result indicates the presence of West Nile virus (WNV) RNA and is consistent with early WNV infection.

Reference Values:
- Negative

ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can also be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources.(5) Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

**Useful For:** Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) using cerebrospinal fluid specimens An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset) This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

**Interpretation:** A positive result indicates the presence of West Nile virus (WNV) RNA and is consistent with early WNV infection.

**Reference Values:**

Negative

**Clinical References:**

**West Nile Virus, RNA, PCR, Molecular Detection, Urine**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans.(1,2,3) Until the virus infection was recognized in 1999 in birds in New York City, WNV had been detected only in the Eastern hemisphere, with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms including headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can also be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time.
Useful For: Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset). The WNV polymerase chain reaction result may remain positive for a longer time in urine than in blood, serum, and cerebrospinal fluid (7 days or more). This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

Interpretation: A positive result indicates the presence of West Nile virus (WNV) RNA and is consistent with early WNV infection.

Reference Values: Negative


FONS 75448

Western blot for anti-optic nerve autoantibodies in the serum

Reference Values: A final report will be provided.

WEEPC 83918

Western Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. The onset may be more abrupt in infants and children than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of male patients with WEE clinical encephalitis, averaging about twice the number of infections detected in female patients. After recovery from the acute disease, patients may require several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.

Useful For: Aiding in the diagnosis of Western equine encephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may
suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**

IgG: <1:1

IgM: <1:1

Reference values apply to all ages.

**Clinical References:**


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**Western Equine Encephalitis Antibody, IgG and IgM, Serum**

**Clinical Information:** The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of male patients with WEE clinical encephalitis, averaging about twice the number of infections detected in female patients. After recovery from acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.

**Useful For:** Aiding the diagnosis of Western equine encephalitis

**Interpretation:** In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG > or =1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis (WEE) and Eastern equine encephalitis (EEE) antigens will show a noticeable cross-reactivity. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age: WEE tends to produce the most severe clinical infections in young persons. Infection in males is primarily due to working conditions and sports activity taking place where the vector is present.


**Reference Values:**

IgG: <1:10  
IgM: <1:10

Reference values apply to all ages.

**Clinical References:**

**Western Ragweed, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to Western ragweed  
Defining the allergen responsible for eliciting signs and symptoms  
Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>0</td>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
**Wheat IgG**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Wheat IgG4**

**Interpretation:**

**Reference Values:**
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

**Wheat, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to wheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Class</th>
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### Whey IgG

**Reference Values:**
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Whey, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to whey Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3</td>
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<td>Strongly positive</td>
</tr>
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Reference values apply to all ages.
White Bean, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to white bean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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White Faced Hornet Venom, IgE, Serum

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Establishing a diagnosis of an allergy to white faced hornet venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
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Reference values apply to all ages.


**White Hickory, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to white hickory Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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</tbody>
</table>

White Pine, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white pine Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

Clinical References: Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd edition. Edited by RA McPherson,
White Potato, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white potato Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy - To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
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<td>&lt;0.10</td>
<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<td>2</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Whole Egg, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. Allergy to egg represents one of the most common causes of food allergy, especially in children. The evaluation for egg-related IgE antibodies can identify up to 95% of individuals at risk for clinical allergic reactions. The most clinically prevalent allergens in egg are found in the egg white, but egg yolk also contains clinically significant specific IgE-binding allergens. The allergenic egg proteins found in egg white include ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3) and lysozyme (Gal d 4). Ovomucoid has been demonstrated to be the most clinically significant egg allergen, in part due to its heat and digestion resistance. In the yolk, the protein alpha-livetin (Gal d 5) is the major allergen and is involved in bird-egg syndrome. Foods that may contain egg include salad dressings, breads, breaded foods, muffins, cakes, marshmallows, prepared soups and beverages, frostings, ice cream and sherbets, pie fillings, sausages, prepared meats, mayonnaise, coatings and breading for fried foods and other sauces. Sensitization to allergic reaction to inhaled egg-white allergens has been reported in egg-processing workers and bakers. Certain vaccines grown on chick embryos may cause severe allergic reactions in patients when injected. Further development of vaccines, most of which are no longer grown on egg protein, seems to have decreased or even eliminated the risk. There is cross-reactivity between chicken egg white and turkey, duck, goose, and gull egg whites. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

Useful For: Establishing a diagnosis of an allergy to whole egg Identifying egg allergens:
- Responsible for allergic disease and/or anaphylactic episode
- To confirm sensitization prior to beginning immunotherapy
Testing for immunoglobulin E (IgE) antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Whole egg includes proteins and potential allergens from both egg white and egg yolk. Egg white is generally more allergenic than egg yolk. Clinical reactions to egg are predominantly IgE-mediated immediate reactions characterized by atopic dermatitis, urticarial (hives), angioedema, vomiting, diarrhea, rhinoconjunctivitis, and asthma. Children with atopic dermatitis may have an immediate exacerbation of symptoms or a delayed reaction causing a worsening of their dermatitis 1 to 2 days after exposure to egg. Eosinophilic esophagitis as a result of allergy to egg has been described. Egg white is often responsible for the early development of urticaria and eczema during infancy. In egg yolk, alpha-livetin (Gal d 5) is the major allergen and allergenicity to Gal d 5 is involved in bird-egg syndrome characterized egg intolerance in adults is due to sensitization by inhalation of bird dander. In these cases, there is secondary sensitization or cross-reactivity with serum albumin in egg yolk (Gal d 5) resulting in potential respiratory symptoms including asthma or rhinitis with bird exposure and additional allergic symptoms to egg. Table of Major Egg Allergens Egg white allergen Common name Heat-and Digestion Stability Allergenic activity Gal d 1 Ovomucoid Stable +++ (major allergen) Gal d 2 Ovalbumin Unstable ++ Gal d 3 Ovotransferrin/conalbumin Unstable + Gal d 4 Lysozyme Unstable ++ Egg yolk allergen Gal d 5 Alpha-livetin, serum albumin Partially stable Gal d 6 YGP42, a lipoprotein Stabile Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com

Wild Rye Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to wild rye grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode - To confirm sensitization prior to beginning immunotherapy

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
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<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.

**Williams Syndrome, 7q11.23 Deletion, FISH, Varies**

**Clinical Information:** Williams syndrome (WS) is a genetic disorder that occurs in 1/20,000 to 1/50,000 live births. Although WS is typically a sporadic disorder, familial cases have been reported. WS is characterized by a variable combination of cardiovascular abnormalities, connective tissue abnormalities, distinct facial features, infantile hypercalcemia, mental retardation, and characteristic social interactions such as extreme friendliness and attention-deficit hyperactivity disorder. Isolated congenital narrowing of the ascending aorta is common in WS patients and results in a separate syndrome called supravalvular aortic stenosis (SVAS). WS is a contiguous gene deletion syndrome, caused by deletion of several genes on chromosome 7q. One gene that often is deleted in WS is the elastin gene, which causes SVAS and other cardiovascular disease in these patients. This association was described by Ewart et al (1993) who identified hemizygosity of the elastin gene in WS and SVAS. The elastin gene, ELN, has been mapped to 7q11.23 (Williams syndrome chromosome region, and is reportedly hemizygous in up to 96% of patients with WS). The deletion of an elastin gene locus cannot be detected by conventional high-resolution chromosome analysis in the vast majority of cases due to the small size of this deletion. Nickerson et al used molecular methods to detect a deletion of the elastin gene in 91% (39/43) of WS patients. In up to 1% of patients, WS is caused by a gene mutation within or near the elastin gene. These mutations would not be detected by this FISH test. FISH testing involves a DNA probe that detects only large deletions including this entire gene and the DNA probe, small deletions or mutations may give normal results by FISH. Patients with a deletion outside of the elastin gene could display normal development of connective tissue, including the heart, but have other features of WS.

**Useful For:** Establishing a diagnosis of Williams syndrome Detecting cryptic rearrangements involving 7q11.23 that are not demonstrated by conventional chromosome studies

**Interpretation:** The use of high-resolution chromosome studies and FISH for Williams syndrome chromosome region should diagnose about 96% of Williams syndrome patients and, at the same time, identify any other chromosome anomalies.

**Reference Values:** An interpretive report will be provided.


**Willow, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to willow Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


WT1 I

Wilms Tumor (WT-1) Immunostain, Technical Component Only

Clinical Information: Wilms tumor-1 (WT-1) protein is a transcription factor that acts as a tumor suppressor gene. WT-1 is involved in differentiation of certain tissues such as mesothelium and the urogenital system. It is also expressed in Wilms tumor, a kidney tumor found in children. In normal tissues, it is expressed in kidney, a subset of hematopoietic cells, Sertoli cells in the testis, granulosa cells in the ovary, and decidual cells of the uterus.

Useful For: Aids in the identification of Wilms tumor

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


WDZ

Wilson Disease, Full Gene Analysis, Varies
**Clinical Information:** Wilson disease (WD) is an autosomal recessive disorder that results from the body's inability to excrete excess copper. Typically, the liver releases excess copper into the bile. Individuals with WD lack the necessary enzyme that facilitates clearance of copper from the liver to bile. As a result, copper accumulates first in the liver and gradually in other organs. The brain, kidneys, bones, and corneas can also be affected. WD affects approximately 1 in 30,000 people worldwide, with a carrier frequency of approximately 1 in 90 individuals. The primary clinical manifestations of WD are hepatic and neurologic. Hepatic disease can be quite variable, ranging from hepatomegaly or other nonspecific symptoms that mimic viral hepatitis to severe liver damage, such as cirrhosis. Neurologic symptoms of WD can include poor fine-motor coordination, ataxia, and dysphagia. Psychiatric manifestations are reported in approximately 20% of individuals with WD. A characteristic ophthalmologic finding is the Kayser-Fleischer ring. Individuals with WD typically begin to show symptoms of liver dysfunction or neurologic disease in the first or second decade of life. If not treated, WD can cause liver failure, severe brain damage, and even death. A variety of laboratory tests are recommended in the initial evaluation for WD. In approximately 95% of cases, serum ceruloplasmin is below normal. Additionally, patients with WD show decreased copper in serum, increased copper in urine, and significantly elevated copper on liver biopsy. While liver biopsy is not recommended as a first-tier screening test for WD, it can be useful to help interpret discrepant biochemical or molecular results. The other tests should be performed prior to sequence analysis of the ATP7B gene, the gene responsible for WD. More than 300 disease-causing mutations have been identified in the ATP7B gene. Most mutations are family-specific with the exception of the H1069Q mutation, which accounts for greater than 50% of identified disease alleles in the Northern European Caucasian population. See Wilson Disease Testing Algorithm in Special Instructions for additional information.

**Useful For:** Diagnostic confirmation of Wilson disease

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**FWING 57955**

**Wingscale (Atriplex Canescens) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 50.00-99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

**WORM 82680**

**Wormwood, IgE, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergy to wormwood

Defining the allergen responsible for eliciting signs and symptoms

Identifying allergens: - Responsible for allergic disease and/or anaphylactic episode

-To confirm sensitization prior to beginning immunotherapy

-To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**XALDZ 35575**

**X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies**

**Clinical Information:** X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease characterized by magnetic resonance imaging (MRI) findings in the white matter, adrenocortical insufficiency, and abnormal plasma concentrations of very long chain fatty acids. The phenotypic expression of X-ALD varies widely. The phenotypes can be subdivided into 3 main categories: childhood cerebral form, adrenomyeloneuropathy (AMN), and Addison disease only. The childhood cerebral form has onset of symptoms between ages 4 and 8, beginning with attention deficit hyperactivity disorder-like symptoms with progressive cognitive, behavior, vision, hearing, and motor deterioration. AMN usually presents in males in their late twenties as progressive paraparesis, sexual dysfunction, sphincter disturbances, and abnormalities in adrenocortical function. The Addison only phenotype typically presents by age 7.5 with adrenocortical insufficiency without significant neurological involvement. Most of these patients eventually develop AMN. Some female carriers may experience mild AMN symptoms with a later age of onset. The phenotype cannot be predicted by very long chain fatty acids (VLCFA) plasma concentration or by the nature of the genetic variant. The same variant can be associated with each of the known phenotypes. Different phenotypes often occur within a family. POX / Fatty Acid Profile,
Peroxisomal (C22-C26), Serum testing is the preferred first-tier screening method for X-ALD. This is abnormal in 99% of affected males and 85% of carrier females. Sequencing of the ABCD1 gene is available to confirm the diagnosis of X-ALD, improve carrier detection, and assist with prenatal diagnosis.

**Useful For:** Confirming a diagnosis of X-linked adrenoleukodystrophy Identifying a variant in the ABCD1 gene

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**X-Linked Hyper IgM Syndrome, Blood**

**Clinical Information:** CD154 (CD40 ligand: CD40L) is required for the interaction of T cells and B cells as part of the normal adaptive immune response. Activation of T cells leads to the expression of the CD40L molecule on the cell surface. CD40L binds the CD40 receptor that is always present on B cells, monocytes, and macrophages (regardless of environmental conditions). This interaction of CD40L with CD40 is important in B-cell proliferation, differentiation, and class-switch recombination (isotype class-switching). Patients with X-linked hyper-IgM (XL-HIGM) syndrome have defective CD40L expression on their activated helper CD4 T cells.(1,2) This leads to defective B-cell responses and the absence of immunoglobulin class-switching. These features are typified in these patients by a profound reduction or absence of isotype class-switched memory B cells (CD19+CD27+IgM-IgD-) with low or absent secreted IgG and IgA, and normal or elevated serum IgM levels.(1,2) Due to the impairment of T-cell function and macrophage activation, XL-HIGM patients are particularly prone to opportunistic infections with Pneumocystis jiroveci, Cryptosporidium, and Toxoplasma gondii.(1) To date, more than 100 unique mutations of CD40LG, the gene that encodes CD40L, have been described, affecting the intracellular, transmembrane and, more commonly, extracellular domain containing the CD40-binding region. A defect in surface expression of CD40L on activated CD4 T cells can be demonstrated using an anti-CD40L antibody and flow cytometry.(3,4) Since certain CD40LG mutations can maintain surface protein expression, albeit with loss of function, it is important to also evaluate CD40L-binding capacity to eliminate the possibility of false-negative results. A soluble recombinant, chimeric receptor protein, CD40-ulg, is incorporated into the assay, which assesses CD40L function by determining receptor-binding activity. Approximately 20% of XL-HIGM patients have activated CD4 T cells with normal surface expression of CD40L, but aberrant function.(4) XL-HIGM is a severe type of primary immunodeficiency that affects males, and most patients are diagnosed within a few months to the first year of life. Females are typically carriers and asymptomatic. Consequently, this test is only indicated in young males (<10 years of age) or, to identify carriers, in females of child-bearing age (<45 years).

**Useful For:** Screening for X-linked hyper-IgM (XL-HIGM) or CD40L deficiency, primarily in male patients younger than 10 years of age Ascertaining XL-HIGM carrier status in females of child-bearing age younger than 45 years of age

**Interpretation:** This is a qualitative assay; CD40L-protein expression and function is reported as...
Absence of CD40L-protein expression and function is consistent with X-linked hyper-IgM (XL-HIGM). In females, the presence of 2 populations-normal and abnormal-is consistent with carrier status. Most patients (80%-90%) with XL-HIGM have absent or significantly reduced CD40L expression on their activated CD4 T cells. Patients with normal CD40L expression, but abnormal function, show an absence of binding with soluble chimeric CD40-uIg antibody, substantiating a diagnosis of XL-HIGM. Females who are carriers for this disease will show a typical bimodal pattern of CD40L expression, with 50% of the T cells lacking any CD40L expression. In the case of aberrant protein function, a similar profile will be obtained with the CD40-uIg antibody. CD69 is a marker for T-cell activation and serves as a positive control; in the absence of induced CD69 expression on T cells, the presence of XL-HIGM cannot be assessed.

Reference Values:
Present

Clinical References:

Y Chromosome Microdeletions, Molecular Detection, Varies

Clinical Information: Yq microdeletions involving some or all of the azoospermic factor (AZF) region are the most frequently identified cause of spermatogenic failure in chromosomally normal men with nonobstructive azoospermia (3%-15%) or severe oligospermia (6%-10%). Among unselected infertile males, the overall frequency of Yq microdeletions is approximately 3%. The relative frequency of Yq microdeletions makes the evaluation for them an important aspect of the diagnostic work up in infertile males, especially those with azoospermia or severe oligospermia. Most cases of Yq microdeletions occur de novo, and due to the consequential infertile phenotype, they are typically not transmitted. However, in cases where assisted reproductive technology (example: testicular sperm extraction followed by intracytoplasmic sperm injection) is used to achieve viable pregnancy, all male offspring born to a microdeletion carrier will carry the deletion and may be infertile. Men testing positive for 1 or more microdeletions who are enrolled in an in vitro fertilization treatment program may wish to consider alternative options to intracytoplasmic sperm injection (eg, donor sperm) and consultation with an experienced reproductive endocrinologist and medical geneticist is recommended. Most Y microdeletions are the result of homologous recombination between repeated sequence blocks. Testing for deletions involves investigating for the presence or absence of markers located within nonpolymorphic regions of the AZF region.

Useful For: Evaluating men with azoospermia, severe oligozoospermia, or otherwise unexplained male factor infertility

Interpretation: An interpretive report will be provided.

Clinical References:

Yellow Faced Hornet Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to yellow faced hornet venom

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Yellow Jacket Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to yellow jacket venom

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
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| 6     | > or =100| Strongly positive Reference values apply to all ages.


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**Yersinia Culture, Feces**

**Clinical Information:** Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Several species of Yersinia that are detected by this test may cause diarrhea. Yersinia enterocolitica is the species most commonly isolated with this test.

**Useful For:** Determining whether Yersinia species may be the cause of diarrhea Reflexive testing for Yersinia species from nucleic acid amplification test-positive feces This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

**Interpretation:** The growth of Yersinia species identifies a potential cause of diarrhea.

**Reference Values:**

No growth of pathogen

**Clinical References:**

**YAP1 70583**

Yes-Associated Protein (YAP) Immunostain, Technical Component Only

**Clinical Information:** Yes-associated protein (YAP) is a downstream regulatory target in the Hippo signaling pathway that is upregulated in sonic hedgehog-associated medulloblastomas and medulloblastomas with activation of the Wnt signaling pathway and is expressed on lung, placenta, prostate, ovary, and testis.

**Useful For:** Identification and differentiation of medulloblastomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FYABS 57847**

Yo Antibody Screen with Reflex to Titer and Western Blot

**Reference Values:**

Yo Ab, IFA: Negative

Purkinje cells cytoplasmic antibody (Yo) can be found in approximately 50% of patients with paraneoplastic cerebellar degeneration (PCD). The presence of Yo antibody strongly suggests underlying gynecological cancer primarily of ovarian or breast origin. A negative assay for Yo antibody does not exclude the possibility of a malignant tumor.

**FYOG 57915**

Yogurt (Lactobacillus bulgaricus) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 ̃ 0.69 Low Positive 2 0.70 ̃ 3.49 Moderate Positive 3 3.50 ̃ 17.49 Positive 4 17.50 ̃ 49.99 Strong Positive 5 50.00 ̃ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Current as of June 14, 2021 12:13 pm CDT**
Useful For: Identification of dendritic cells and classification of histiocytic disorders

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


MZIKV 65275

Zika Virus IgM Antibody Capture ELISA, Serum

Clinical Information: Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias, and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the Food and Drug Administration (FDA). The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding Centers for Disease Control and Prevention (CDC) testing guidelines visit www.cdc.gov/zika/. These guidelines are reflected in Assessment for Zika Virus Infection Special Instructions: Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

Useful For: Screening for the presence of IgM-class antibodies to Zika virus

Interpretation: See Assessment for Zika Virus Infection in Special Instructions for a review of the recommended testing and interpretation of results. For the most recent Centers for Disease Control and Prevention (CDC) guidelines for Zika virus testing visit www.cdc.gov/zika/. Presumptive Zika Positive: IgM-class antibodies to Zika virus (ZIKV) detected. This is a preliminary result and does not confirm evidence of ZIKV infection. Confirmatory testing may be required as determined by your local health department. A False-positive results may occur in patients with other current or prior flavivirus infections (eg, dengue virus). For patients with less than 7 days of symptoms or last possible exposure to ZIKV, reverse transcription-polymerase chain reaction (RT-PCR) for ZIKV on serum and urine is recommended. A positive ZIKV RT-PCR result on either specimen is confirmatory for ZIKV infection. Other Flavivirus Positive: Antibodies to a flavivirus, not ZIKV, were detected. Consider targeted testing for IgM-class antibodies to dengue and/or West Nile viruses as appropriate, taking into consideration patient exposure...
and presentation. Negative: No evidence of IgM-class antibodies to ZIKV. For specimens collected less than 7 days post symptom onset or possible ZIKV exposure, RT-PCR for ZIKV on serum and urine to exclude a false-negative ZIKV IgM result is recommended. For symptomatic patients with travel to dengue endemic areas, testing for IgM antibodies to dengue virus is also recommended.

Reference Values:
Negative

Clinical References:

Zika Virus, PCR, Molecular Detection, Random, Urine

Clinical Information:
Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the Food and Drug Administration (FDA). The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding CDC testing guidelines visit www.cdc.gov/zika/. These guidelines are reflected in Assessment for Zika Virus Infection in Special Instructions. Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

Useful For:
Qualitative detection of Zika virus RNA in paired urine and serum from individuals meeting CDC Zika virus clinical or epidemiologic criteria

Interpretation:
A positive test result indicates the presence of Zika virus RNA in the specimen. The FDA requires that urine specimens be tested in conjunction with a paired serum specimen. However, a positive result in either specimen is consistent with recent infection. A negative test result with a positive internal control indicates that Zika virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of PCR inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:
Negative

Clinical References:
Zika Virus, PCR, Molecular Detection, Serum

Clinical Information: Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the Food and Drug Administration (FDA). The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding CDC testing guidelines visit www.cdc.gov/zika/. These guidelines are reflected in Assessment for Zika Virus Infection in Special Instructions: Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

Useful For: Qualitative detection of Zika virus RNA in serum from individuals meeting CDC Zika virus clinical or epidemiologic criteria

Interpretation: A positive test result indicates the presence of Zika virus RNA in the specimen. A negative test result with a positive internal control indicates that Zika virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of PCR inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:

Negative


Zinc Protoporphyrin, Blood

Clinical Information: The porphyrins are intermediaries in the heme synthesis pathway. When iron is not available for heme synthesis (eg, iron deficiency), zinc protoporphyrin (ZPP) accumulates within RBCs. Lead inhibits several enzymes in the heme synthesis pathway and causes increased levels of RBC ZPP. ZPP is a biological marker of lead toxicity and was previously used, in conjunction with blood lead assays, to screen for lead poisoning in children. However, because of poor sensitivity and specificity, ZPP is no longer recommended for lead screening in children. However, ZPP remains a useful tool for monitoring treatment of individuals with confirmed elevated lead levels.

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com
Useful For: Evaluating iron deficiency Monitoring treatment and environmental intervention of chronic lead poisoning

Interpretation: An elevated zinc protoporphyrin (ZPP) indicates impairment of the heme biosynthetic pathway. Elevated ZPP levels in adults may indicate long-term (chronic) lead exposure or may be indicative of iron deficiency anemia or anemia of chronic disease.

Reference Values:
<70 mc mol ZPP/mol heme


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**Zinc Transporter 8 (ZnT8) Antibody, Serum**

**Clinical Information:** Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus since the 1970s. Since 1988, several autoantigens against which islet antibodies are directed have been identified. These include the insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin, and, most recently, the zinc transporter ZnT8. Only 4% to 7% of patients with type 1 diabetes are autoantibody negative, fewer than 10% have only 1 marker, and around 70% have 3 or 4 markers. These findings have been confirmed in multiple specialty laboratories internationally. One or more of these autoantibodies are detected in 93% to 96% of patients with type 1 diabetes, both adults and children. These antibodies are also detectable in relatives of type 1 diabetic patients at risk for developing diabetes, before clinical onset. Because of symptom-onset in adulthood, societal obesity, and initial insulin-independence, some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes. These patients with either "latent autoimmune diabetes in adulthood" or type 1 diabetes mellitus, may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies, including ZnT8 antibody. (2-5) Patients with gestational diabetes can also be stratified for future diabetes risk by detection of 1 or more islet autoantibodies (including ZnT8 antibody).

Useful For: Clinical distinction of type 1 from type 2 diabetes mellitus Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes, and those with gestational diabetes) Prediction of future need for insulin treatment in adult-onset diabetic patients

**Interpretation:** Seropositivity for ZnT8 autoantibody (> or =15 IU/mL) is supportive of: -A diagnosis of type 1 diabetes -A high risk for future development of diabetes -A current or future need for insulin therapy in patients with diabetes

**Reference Values:** <15.0 U/mL

ZNU 8591

**Zinc, 24 Hour, Urine**

**Clinical Information:** Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet (excess copper or iron interfere with absorption) or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition), or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Identifying the cause of abnormal serum zinc concentrations using a 24-hour urine specimen

**Interpretation:** Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 20 to 967 mcg/24 hours. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

**Reference Values:**
- 0-17 years: not established
- > or =18 years: 109-1,476 mcg/24 hours

**Clinical References:**

ZNS 8620

**Zinc, Serum**

**Clinical Information:** Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. The peptidases, kinases, and phosphorylases are most sensitive to zinc depletion. Zinc is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet (excess copper or iron interfere with absorption) or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition), or because the zinc in the diet is bound to phytate (fiber) and not available for absorption. Excess copper and iron in the diet (eg, iron supplements) interfere with zinc uptake. Once absorbed, the most common route of loss is via exudates from open wounds or gastrointestinal loss. Zinc depletion occurs in burn patients who lose zinc in the exudates from their burn sites. Hepatic cirrhosis causes excess loss of zinc by enhancing renal excretion. Other diseases
that cause low serum zinc are ulcerative colitis, Crohn disease, regional enteritis, sprue, intestinal bypass, neoplastic disease, and increased catabolism induced by anabolic steroids. The conditions of anorexia and starvation also result in low zinc levels. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Detecting zinc deficiency

**Interpretation:** Normal serum zinc is 0.66 to 1.10 mcg/mL. Burn patients with acrodermatitis may have zinc as low as 0.4 mcg/mL; these patients respond quickly to zinc supplementation. Elevated serum zinc is of minimal clinical interest.

**Reference Values:**
- 0-10 years: 0.60-1.20 mcg/mL
- > or =11 years: 0.66-1.10 mcg/mL

**Clinical References:**

**Zinc/Creatinine Ratio, Random, Urine**

**Clinical Information:** Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet (excess copper or iron interfere with absorption) or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Identifying the cause of abnormal serum zinc concentrations using a random urine specimen

**Interpretation:** Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 89 to 910 mcg/g creatinine. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

**Reference Values:**
- 0-17 years: not established
- > or =18 years: 89-910 mcg/g Creatinine

**Clinical References:**

FZIP 57107

Ziprasidone (Geodone, Zeldox)

Reference Values:
Units: ng/mL

Expected plasma concentrations in patients taking Recommended Daily Dosages: Up to 220 ng/mL

FZOLP 57738

Zolpidem (Ambien), serum or plasma

Reference Values:
Units: ng/mL

Expected hypnotic zolpidem concentrations in patients taking recommended daily dosages: up to 250 ng/mL.

Toxic range has not been established.

ZONI 83685

Zonisamide, Serum

Clinical Information: Zonisamide (Zonegrán) is approved as adjunctive therapy for partial seizures refractory to therapy with traditional anticonvulsants. Zonisamide is the pharmacologically active agent; metabolites are not active. Essentially 100% of the zonisamide dose is absorbed. Zonisamide binds to erythrocytes; approximately 88% of circulating zonisamide is bound in erythrocytes. Because the erythrocyte-bound zonisamide is inactive, and binding varies with blood concentration, the relationship between serum level and dose is not linear. Time to peak zonisamide concentration is 2 to 4 hours; time to peak is delayed by co-administration with food to 4 to 6 hours. Zonisamide is metabolized by N-acetyl transferase (NAT1), cytochrome P450 3A4 (CYP3A4), and uridine diphosphate glucuronidation (UDPG). Zonisamide is eliminated in the urine predominantly as the parent drug (35%), N-acetyl zonisamide (15%), and as the glucuronide ester of reduced zonisamide (50%). Co-administration of drugs that affect NAT1, CYP3A4, and UDPG activity, such as phenytoin and carbamazepine, will decrease zonisamide concentration. A typical zonisamide dose administered to an adult is 400 to 600 mg/day, administered in 2 divided doses. The apparent volume of distribution of zonisamide is 1.5 L/kg. Approximately 40% of the zonisamide circulating in the serum is bound to proteins. Zonisamide protein binding is unaffected by other common anticonvulsant drugs. The elimination half-life from plasma is 50 to 60 hours; the elimination half-life from erythrocytes is over 100 hours. Since zonisamide is cleared predominantly by the kidney, the daily dosage of zonisamide given to patients with a creatinine clearance below 20 mL/min should be reduced. (1,2) Serum level monitoring is recommended for all patients to ensure appropriate dosing because: 1) patient response correlates with serum level, 2) serum level does not correlate with dose because of concentration-dependent erythrocyte binding, 3) elimination is affected by co-administration of drugs that affect NAT1, CYP3A4, and UDPG, and 4) renal function affects elimination. The most common toxicity associated with excessive serum level is drowsiness. Adverse effects not related to serum level include rash, increased serum creatinine and alkaline phosphatase, kidney stone formation, and bruising.

Useful For: Monitoring zonisamide therapy; recommended for all patients to ensure appropriate dosing Assessing medication compliance

Current as of June 14, 2021 12:13 pm CDT 800-533-1710 or 507-266-5700 or mayocliniclabs.com Page 2650
Interpretation: Steady-state zonisamide concentration in a trough specimen collected just before next dose correlates with patient response but not with dose. Optimal response to zonisamide occurs when trough zonisamide concentration is in the range of 10 to 40 mcg/mL. Peak serum concentration for zonisamide occurs 2 to 6 hours after dose, and time to peak is affected by food intake. Because carbamazepine activates glucuronidation, patients taking carbamazepine concomitantly with zonisamide have significantly lower zonisamide concentrations compared to patients on the same dose not receiving carbamazepine.

Reference Values: 10-40 mcg/mL


FZCCE 57562

Zucchini (Cucurbita spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 ≤kU/L <0.69 Low Positive 2 0.70 ≤kU/L <3.49 Moderate Positive 3 3.50 ≤kU/L <17.49 Positive 4 17.50 ≤kU/L <49.99 Strong Positive 5 50.00 ≤kU/L <99.99 Very Strong Positive 6 ≥99.99 Very Strong Positive

Reference Values: <0.35 kU/L

MULT 35577

Zygosity Testing (Multiple Births), Varies

Clinical Information: Approximately 30% of twins are monozygotic (identical), while 70% are dizygotic (nonidentical or fraternal). Monozygotic twins originate from a single egg and, by definition, have identical DNA markers throughout their genomes. Dizygotic twins, on the other hand, inherit their genetic complement independently from each parent and are no more likely to have genetic material in common than are any other full siblings. Polymorphic DNA markers have been identified. DNA markers are regions of DNA that display normal variability in the type or the number of nucleotide bases at a given location. One particular class of repetitive DNA that exhibits marked variability is microsatellites. With the use of such markers, it is possible to distinguish one individual from another because of differences detected at these polymorphic loci. Utilizing PCR followed by capillary electrophoresis, the genotypes of a set of twins (triplets, etc.) are derived from the analysis of multiple markers. This genotype is compared to those of their parents to determine if the children are mono- or dizygotic. Any differences detected between siblings' microsatellite markers indicate dizygosity. Many disorders are known to occur on a genetic basis though the genes have not been identified for all of them. If one member of a set of twins is diagnosed with a genetic disorder, determination of zygosity, in addition to other testing, may provide additional information regarding risk assessment of unaffected individuals. In addition, zygosity can be useful when evaluating for twin-twin transfusion syndrome during pregnancy or as part of a preorgan transplant workup for situations where one twin is donating an organ to another twin.

Useful For: Determining genetic risk for an individual whose twin or triplet is affected with a genetic disorder for which a specific genetic test is not available (or such testing is uninformative) Assessment of risks prenatally when one fetus of multiples is known to be affected by a specific disorder Organ or bone marrow transplantation compatibility testing Familial or parental interest
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Clinical Information:**
Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. In conditions of increase glandular size and tissue damage, PSA is released into circulation. Measurement of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment. PSA is also used as a screening tool for prostate cancer detection, although its use in screening has become controversial in recent years. While an elevated serum PSA is associated with prostate cancer, a number of benign conditions, such as benign prostatic hyperplasia (BPH) and prostatitis might lead to elevated serum PSA concentrations. As a consequence, PSA lacks specificity for prostate cancer detection. Several PSA isoforms have been identified that can further increase the specificity of PSA for prostate cancer. In particular, the [-2] form of proPSA (p2PSA) shows improved performance over either total or free PSA for prostate cancer detection on biopsy. The prostate health index (phi) is a formula that combines all 3 PSA forms (total PSA, free PSA, and p2PSA) into a single score. phi is calculated using the following formula: (p2PSA/free PSA) x square root (PSA). In a multicenter study that compared the performance of PSA, free PSA, p2PSA, and phi in men undergoing prostate biopsy due to a serum PSA concentration between 4 and 10 ng/mL, phi was the best predictor of any prostate cancer, high-grade cancer, and clinically significant cancer. At 95% clinical sensitivity, the clinical specificity of phi was 16.0%, compared to 8.4% for free PSA and 6.5% for PSA. Prostatic biopsy is required for diagnosis of cancer.

**Useful For:**
Aids in distinguishing prostate cancer from benign prostate conditions in men 50 years of age and older with prostate-specific antigen (PSA) results in the 4 to 10 ng/mL range and digital rectal examination (DRE) findings that are not suspicious for cancer

**Interpretation:** The prostate health index (phi) may be used to determine the probability of prostate cancer on biopsy in men 50 years of age and older with prostate-specific antigen (PSA) in the 4 to 10 ng/mL range. Low phi scores are associated with a lower probability of finding prostate cancer on biopsy, and higher phi scores are associated with an increased probability of finding prostate cancer on biopsy. The choice of an appropriate phi score to be used in guiding clinical decision making may vary for each patient and may depend on other clinical factors or family history. The table below indicates the probability of finding prostate cancer on biopsy when PSA is the in range of 4 to 10 ng/mL and may be used as guidance for interpreting the phi score. phi range Probability of cancer 95% Confidence interval
0.0-26.9 9.8% 5.2%-15.4% 27.0-35.9 16.8% 11.3%-22.2% 36.0-54.9 33.3% 26.8%-39.9% 55.0+ 50.1% 39.8%-61.0%

**Reference Values:**

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<td>Free PSA Range</td>
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<td>----------------</td>
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<tr>
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<td>&gt; 80 Years</td>
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% Free PSA **Probability of Cancer**

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<th>Free PSA Range</th>
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Prostate Health Index (phi) **Males:**

<table>
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<th>Probability of Cancer</th>
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<tbody>
<tr>
<td>0-26.9</td>
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<tr>
<td>27.0-35.9</td>
<td>16.8%</td>
<td>11.3-22.2%</td>
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<td>36.0-54.9</td>
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<td>&gt;55.0</td>
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**Clinical References:**